

EPA Jacket 100-902

Vol.2



U.S. ENVIRONMENTAL PROTECTION AGENCY
Office of Pesticide Programs
Registration Division (7505C)
1200 Pennsylvania Ave., NW
Washington, D.C. 20460

EPA Reg. Number:

100-902

Date of

APR 12 2006

Term of Issuance:

Conditional

Name of Pesticide Product:

Emamectin Benzoate
Technical

NOTICE OF PESTICIDE:

☒ Registration
☐ Reregistration

(under FIFRA, as amended)

Name and Address of Registrant (include ZIP Code):

Carolyn Brinkley
Syngenta Crop Protection, Inc.
PO Box 18300
Greensboro, NC 27419

Note: Changes in labeling differing in substance from that accepted in connection with this registration must be submitted to and accepted by the Registration Division prior to use of the label in commerce. In any correspondence on this product always refer to the above EPA registration number.

On the basis of information furnished by the registrant, the above named pesticide is hereby registered/reregistered under the Federal Insecticide, Fungicide and Rodenticide Act.

Registration is in no way to be construed as an endorsement or recommendation of this product by the Agency. In order to protect health and the environment, the Administrator, on his motion, may at any time suspend or cancel the registration of a pesticide in accordance with the Act. The acceptance of any name in connection with the registration of a product under this Act is not to be construed as giving the registrant a right to exclusive use of the name or to its use if it has been covered by others.

The above product was conditionally registered on 5/19/99 with an expiration date of 5/1/02. One of the conditions of registration of the initial products was that the registrant must conduct an estuarine/marine invertebrate life-cycle study (OPPTS GLN 850.1350). The registration deadline was extended until 5/1/06 to allow for submission and review of this study. The study included in the analysis of pome fruit as a new use. The study was classified as "supplemental" but since it provides enough information for a risk analysis it has been determined to satisfy the guideline requirement. Since the data requirements for the original registration have been satisfied the time limitation of the registration is removed with this registration notice.

Signature of Approving Official:

Date:

Thomas C. Harris, Biologist
Insecticide-Rodenticide Branch
Registration Division (7504C)

APR 12 2006

This copy
for S167



U.S. ENVIRONMENTAL PROTECTION AGENCY
Office of Pesticide Programs
Registration Division (7505C)
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Signature of Approving Official:

Date:

Thomas C. Harris, Biologist
Insecticide-Rodenticide Branch
Registration Division (7504C)

APR 12 2006

MEETING NOTES

topic:

Ornament 28 day intake

| | |
|--|------------------------|
| date: <i>4/4/06</i> | location: <i>910 J</i> |
| attendees: | |
| purpose: <i>1) dose levels</i> <i>2) mouse strain</i> | |

ACTION ITEMS:

- * if Sigm wants EPA comment on dose selection then EPA needs more data
- * mouse notes
- * KR write email \rightarrow TD \rightarrow CB

NEXT MEETING:

NOTES:

1) dose levels

Q proposed: *0.1 mg/l*
0.5
2.5

need *0* mg/l
in range *1*
funding *5*
10
25
125

A - we can't tell from info given
probably want one higher
* we need data to comment

2) mouse strain

Q proposed: wild type CF-1 mouse, Charles River Lab *NO*; used heterozygotes by our tech
R - pop - or 2 studies to -
issue: some mice have a mutant *have a mutant*
have a mutant *glycoprotein which acts as a transport across blood/brain barrier*
+ transports in & out
- transports in only so builds up
Pgp also involved in anti-cancer drug transport



carolyn.brinkley@syngenta.com

03/31/2006 01:48 PM

To Thomas Harris/DC/USEPA/US@EPA

simon.chivers@syngenta.com, tim.pastoor@syngenta.com,
cc charles.breckenridge@syngenta.com,
amechi.chukwudebe@syngenta.com

bcc

Subject Emamectin Inhalation Study Questions - EPA Meeting Not Needed

Dear Tom,

When we requested a meeting with HED to discuss this study, we had concerns about achieving low inhalation chamber concentrations of emamectin, using technical grade emamectin. We were not sure that we could reliably achieve low concentrations and were eager to discuss alternatives so that we could get on with the study. However, we now believe that we can achieve low concentrations of emamectin based upon results from our ongoing project with abamectin and **we don't believe the meeting scheduled for April 4th is needed.**

- We would appreciate HED's response regarding the acceptability of the dose levels and the strain of mouse that we intend to use in this study. We think this can be handled via e-mail or via a conference call with HED if necessary.
- Since we can't begin the study until we have HED's reply, do you think it would be possible to have their response within the next week?

HERE ARE THE DETAILS:

- We intend to use the standard protocol for a 90-day inhalation study. A copy of the protocol is attached for reference <<MM0234-Protocol-Main-V1.doc>>
- We plan to use technical emamectin at concentrations of 0.1, 0.5, and 2.5 ug/L. These levels are anticipated to produce effects (nasal turbinate histopathological changes and clinical signs) at the high concentration (2.5 ug/L) and no effect at the lowest concentration (0.1 ug/L).
- We intend to use the currently available wild type CF-1 mouse, as supplied by Charles River Laboratories, which was used in the 5-day preliminary inhalation toxicity study. Attached is a brief document that summarizes the history of this strain in avermectin toxicity testing, the polymorphic nature of the p-glycoprotein (p-gp) coding gene in this strain, and the ramifications of p-glycoprotein status on avermectin toxicity testing.

<<EMAMECTIN choice of CF-1 mouse strain v2.doc>>

H

If HED has any questions or comments about the dose levels or the rationale for strain selection, please let me know. We can set up a telephone conference if needed.

Thanks for forwarding this to HED. We will await HED's response before starting the study.

Carolyn F. Brinkley

Sr. Regulatory Product Manager / Insecticides

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Email: carolyn.brinkley@syngenta.com MM0234-Protocol-Main-V1.doc EMAMECTIN choice of CF-1 mouse strain v2.doc



Rick Whiting/DC/USEPA/US
03/21/2006 03:29 PM

To: Thomas Harris/DC/USEPA/US@EPA
cc
bcc
Subject: Re: acute tox reviews: emamectin

Tom,

Here is what I found:

100-902 Technical - previous EPA Reg. No. 618-108 - I found two MRID Nos. referencing a number of studies conducted on rats & mice. The studies were reviewed by HED.

- 4274 Lankas, G. (1992) L-656,748: Acute Oral and Intravenous Toxicity Studies in Mice
3612 and Rats: TT #88-043-0, 88-2569, 88-2581, 88-2595: Lab Project Number:
618-244-TOX08. Unpublished study prepared by Merck & Co., Inc. Merck Research
Labs. 32 p.
- 4400 Lankas, G. (1994) L-656,748: Acute Oral Toxicity Study in Rats: Amended Report:
7915 Lab Project Number: 88-043-0. Unpublished study prepared by Merck Institute for
Therapeutic Research. 29 p.



TXR 011310.pdf

100-903 Denim (EC) - previous EPA Reg. No. 618-107
100-904 Proclaim (G) - previous EPA Reg. No. 618-108

In addition to the two MRIDs listed above, I found three additional MRID Nos. These studies were reviewed by CDPR.

- 4385 Bagdon, W. (1994) MK-0244 EC (L-656,748-049C): Acute Ocular Irritation Study in
0112 Rabbits: Lab Project Number: TT# 94-2517. Unpublished study prepared by Merck
Research Labs. 19 p.
- 4386 Labbe, R. (1994) MK-0244: An Acute Inhalation Range-Finding and Toxicity Study
8101 in the Albino Rat: Lab Project Number: TT #93-9011: 90642B. Unpublished study
prepared by BioResearch Labs, Ltd. 187 p.
- 4386 Labbe, R. (1994) MK-0244: An Acute Inhalation Toxicity Study in the Albino Rat:
8102 Lab Project Number: TT #93-9017: 90901: 90642B. Unpublished study prepared by
BioResearch Labs, Ltd. 147 p.



618-00106.wpd 618-00107.wpd

I don't know if this is of any use to you but I noticed that the title of the HED review was for 618-EUP-RU and that TRB had a document for 618-EUP-14. The citation for the study reviewed is as follows:

- 4386 Bagdon, W. (1994) MK-0244 (L-656,748-052S): Acute Dermal Toxicity Study in

9401 Rats; Lab Project Number: TT #94-2918. Unpublished study prepared by Merck Research Labs. 27 p.



618-EUP-00014.wpd

Rick Whiting
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*full doc is 93 pages
elec copy of Thoms*

(FICHE)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

NOV 3 1994

011310

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Emamectin; MK-0244 EC Insecticide; 618-EUP-RU; PP #3G04239; Temporary Tolerances for MK-0244 and its Photoproducts at 0.025 ppm in/on Cole Crops (Cabbage, Broccoli, Brussels Sprouts, and Cauliflower) and Leafy Vegetables (Celery and Lettuce);

P.C. Code No.: 122806
MRID No.: several
DP Barcode No.: D192200,
D194567
Submission No.: S442382,
S446198

TO: George LaRocca/Linda Arrington, PM #13
Insecticide-Rodenticide Branch
Registration Division (H7505C)

FROM: William Dykstra, Ph.D., Toxicologist
Review Section I
Toxicology Branch I *William Dykstra 10/11/94*
Health Effects Division (H7509C)

JD **THRU:** Roger Gardner, Section Head, Toxicologist *Annella McHaleley*
Review Section I
Toxicology Branch I
Health Effects Division (H7509C) *10/11/94 KB 10/17/94*

ACTION REQUESTED: The Registrant, Merck & Co., has submitted a number of toxicology studies to support the requested 1.47 acre, 10 state EUP and temporary tolerances for MK-0244 (Emamectin) and its photoproducts in/on cole crops and leafy vegetables at 0.025 ppm. Additionally, the Registrant is requesting waivers of the

10893

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21-day dermal toxicity study in rabbits with the technical (a 24-day dermal toxicity study is available with the MK-0244 EC formulation) and the eye irritation study with MK-0244 EC formulation. Merck is citing previously submitted eye irritation studies for abamectin formulated product (Avid 1.6 EC) (Guideline Reference 81-4) as an acceptable substitute for an eye irritation study with MK-0244 EC. The eye irritation study with the abamectin formulated product had a Label Signal Word of Warning.

The Registration Division requests that Toxicology Branch-I (TB-I) address the waivers and EUP request by the Registrant and identify the requirements for essential additional toxicology studies which are needed to assess the human health risks associated with this EUP and temporary tolerances. The studies reviewed are acute, subchronic, neurotoxic, developmental, reproduction, and chronic studies performed with technical MK-0244 or formulation, MK-0244 0.16 EC, and were used to determine if the EUP program and temporary tolerances on cole crops and leafy vegetables can be toxicologically supported.

CONCLUSIONS: The EUP and temporary tolerances can be toxicologically supported.

Due to the severe eye injury and trauma to the rabbits in the primary eye irritation study with MK-0244 technical, it is likely that the Label Signal Word for MK-0244 EC will be Danger. For humane reasons, the Registrant is required to use a Label Signal Word of Danger, rather than the proposed Label Signal Word of Warning, for eye injury, plus appropriate precautionary labelling, in lieu of performing a primary eye irritation study with MK-0244 EC. The 21-day dermal toxicity study with technical MK-0244 can be waived, since the 24-day dermal toxicity study with the MK-0244 EC is acceptable for this requirement.

The margins of exposure for EUP farm workers who are involved in the 147 acre EUP program range from 30,000 to 342,860 according to exposure estimates provided by OREB (memo of July 12, 1994, attached) in comparison to the NOEL of 2.4 mg/kg/day in the 24-day dermal toxicity study in rabbits with the formulation. However, according to OREB, worker exposure for full registration is likely to be 200x the exposure estimates for the 147 acre EUP and MOEs would be considerably less for full registration.

Decoxyavermectin has been presented to the Less-than-Lifetime Committee (9/20/94). The Committee recommended the following endpoints to be used for risk assessment:

- (1) The NOEL of 0.075 mg/kg/day (L-660,599) from the 15-day dietary CF-1 mouse study for acute dietary risk assessment.

6/13/0

(2) The NOEL of 2.4 mg/kg/day (MK-0244) from the 24-day dermal study for occupational, residential and farm worker risk assessments for acute and subchronic dermal exposures (1-7 days and 7 days to several months).

(3) A Provisional RfD of 0.00025 mg/kg/day based on NOEL of 0.25 mg/kg/day in one year dog study and an uncertainty factor of 1000. A final RfD will be determined by the RfD Committee when the data base is finalized.

The following list gives studies that are required for the EUP and the temporary tolerances. Those studies that are satisfied are indicated. Additional studies that were submitted by the Registrant which are not required for the EUP and temporary tolerances, but are required for full registration and permanent tolerances are also included in this list. Other special studies which were submitted by the Registrant but are not Guideline requirements are not included in the requirement list.

| <u>Technical Material</u> | | <u>Required</u> | <u>Satisfied</u> |
|---------------------------|---|------------------|------------------------|
| 81-1 | Acute Oral Toxicity | Yes | Partially ¹ |
| 81-2 | Acute Dermal Toxicity | Yes | No ⁶ |
| 81-4 | Primary Eye Irritation | Yes | Yes |
| 81-5 | Primary Dermal Irritation | Yes | Yes |
| 81-6 | Dermal Sensitization | Yes ² | Yes |
| 81-8 | Acute Mammalian Neurotoxicity | Yes ² | Yes |
| 82-1(a) | Subchronic Oral (rodent) | Yes | Yes |
| 82-1(b) | Subchronic Oral (non-rodent) | Yes | Yes |
| 82-2 | 21-Day Dermal | Yes | Waived ³ |
| 82-7 | Subchronic Mammalian Neurotoxicity | Yes ² | Yes |
| 83-1(a) | Chronic Feeding Study (rodent) | Yes ² | Yes |
| 83-1(b) | Chronic Feeding Study (non-rodent) | Yes ² | Yes |
| 83-3(a) | Teratology (first species) | Yes | Yes |
| 83-3(b) | Teratology (second species) | Yes ² | Yes |
| 83-4 | Multigeneration Reproduction | Yes ² | Yes |
| 83-6 | Developmental Neurotoxicity | Yes ² | Yes |
| 84-2(a) | Mutagenicity - Gene Mutation | Yes | Yes ⁴ |
| 84-2(b) | Mutagenicity - Structural Chromosomal Aberrations | Yes | Yes |
| 84-2(c) | Mutagenicity - Other Genotoxic Effects | Yes | Yes |
| 85-1 | Metabolism | Yes ² | Yes |

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Formulation: MK-0244 0.16 EC Insecticide

| | | <u>Required</u> | <u>Satisfied</u> |
|------|---------------------------|------------------|---------------------|
| 81-1 | Acute Oral Toxicity | Yes | Yes |
| 81-2 | Acute Dermal Toxicity | Yes | Yes |
| 81-3 | Acute Inhalation Toxicity | Yes | Yes |
| 81-4 | Primary Eye Irritation | Yes | Waived ⁵ |
| 81-5 | Primary Dermal Irritation | Yes | Yes |
| 81-6 | Dermal Sensitization | Yes | Yes |
| 82-2 | 21-Day Dermal | Yes ² | Yes |

Comments:

1. Only females were tested. This study was graded Core Supplementary and may be upgraded to acceptable if data are provided which indicate that females are the most sensitive sex.
2. Not required for the EUP and temporary tolerance but will be required for registration and permanent tolerances.
3. This study is waived because an acceptable 24-day dermal study on the 1.94% formulation is available.
4. Some of these studies were also conducted on metabolites, polar degradates and isomers as well.
5. This study will be waived if the Registrant changes the signal word to Danger and provides the appropriate precautionary statement for the Danger signal word.
6. No acute dermal study was submitted for the Technical material. This study will not hold up the approval of the temporary tolerance and EUP, however, it will be required for full registration.

The following studies will be required for full registration:

- (a) Upgrading of rat developmental neurotoxicity study with MK-0244 from Supplementary to Minimum.
- (b) Dermal penetration study with MK-0244 or MK-0244 EC.
- (c) Rat and mouse carcinogenicity studies with MK-0244.
- (d) Upgrading acute oral study and submission of acute dermal study with MK-0244.

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In addition, in consideration of farm workers (mixer/loaders and applicators), due to the low NOEL's for this chemical and to the observation that the brain, spinal cord and sciatic nerve are target organs in several species tested by the oral route and in the rabbit by the dermal route, TB-I is concerned about possible accidental exposure to the liquid formulation. TB-I suggests that the Registrant consider substituting the liquid formulation with a water-soluble solid packet. TB-I also requests that the label Signal Word be evaluated from the contents of the packet and that the precautionary statements include "Excessive exposure may result in permanent brain or nerve damage". Appropriate first aid statements are also required.

The Data Evaluation Records (DER'S) for all of the submitted studies are attached.

5



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L0001041

VIA FEDERAL EXPRESS

March 2, 2006

Document Processing Desk [6(a)(2)]
Office of Pesticide Programs (7504C)
U.S. Environmental Protection Agency
Crystal Mall #2, Room 266A
1801 South Bell Street
Arlington, VA 22202-4501

100-902

SUBJECT: SUBMISSION OF DATA UNDER FIFRA SECTION 6(a)(2) – 5 Day Preliminary Inhalation Study in CF-1 Mice With Emamectin Benzoate

In accordance with the Agency's current interpretation of FIFRA Section 6(a)(2) reporting requirements, Syngenta Crop Protection, Inc. is providing certain information from a 5-day preliminary study in wild type CF-1 (BR) mice with emamectin benzoate technical. In this study, CF-1 mice (2 males and 2 females per group) were exposed nose-only (0, 1, 5, 10, 25 or 125 $\mu\text{g}/\text{liter}$) for six hours per day for up to five days.

The following compound-related histopathological findings were observed in the nasal cavity and larynx: Degeneration of the olfactory epithelium in the dorsal medial meatus was seen in all dose groups, with gradually increasing incidence and severity as dose levels increased. Inflammation of the vomeronasal gland of the nasal cavities and laryngeal mucosal epithelial erosion were seen in highest dose group only. In addition, weight loss and adverse clinical signs that are consistent with this chemical class (including those indicative of neurotoxicity) were observed. These histopathological findings are new information and the route of administration (inhalation) is different than previously tested and therefore constitutes new information.

Sincerely yours,

Carolyn F. Brinkley
Sr. Regulatory Product Manager
Regulatory Affairs



carolyn.brinkley@syngenta.com

08/11/2005 11:23 PM

To Thomas Harris/DC/USEPA/US@EPA, Paula
Deschamp/DC/USEPA/US@EPA

cc

bcc

Subject Enamectin 28-day Inhal Study Conf Call Summary &
Exposure Proposa I

Thanks to you and your colleagues for a very beneficial conference call last Thursday. Syngenta appreciates the HED's willingness to talk directly with our scientists regarding the study protocol. Syngenta's summary of the conference call is attached. (Tom, our summary includes a bit more detail that the EPA summary you sent to me. Otherwise there is no difference).

In addition to the conference call summary, the cover letter includes Syngenta's proposal and rationale for exposure intervals of 2 hours in the AM and 2 hours in the PM with a non exposure period in between. You will recall that the HED agreed to discuss this proposal with their colleagues in OREB and let Syngenta know if this is acceptable.

Thanks again for your willingness to have this scientist to scientist discussion. It was very productive.

1. Cover letter - <<Ltr to EPA sum of conf call re study protocol & dates.doc>>
2. Conference Call Summary <<Summary of 8-4-05 conf call to EPA re study protocol & dates.doc>>

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Ltr to EPA sum of conf call re study protocol & dates.doc



Summary of 8-4-05 conf call to EPA re study protocol & dates.doc



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August 11, 2005

Mr. Thomas Harris
Registration Division
Insecticide-Rodenticide Branch
Office of Pesticide Programs (7504C)
U.S. Environmental Protection Agency
Ariel Rios Building
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460

**SUBJECT: EMAMECTIN BENZOATE
SUMMARY OF 8/04/05 TELEPHONE CONFERENCE TO DISCUSS
28-DAY INHALATION STUDY IN CF-1 MOUSE**

Dear Mr. Harris:

As a condition of the registration of Proclaim® Insecticide (EPA Reg. No. 100-904) on certain vegetables, the EPA is requiring a 28-day inhalation study with emamectin benzoate in the CF-1 mouse. On August 4, 2005 representatives of Syngenta Crop Protection, Inc. and the EPA discussed the details of this study via telephone conference call. A summary of the discussion and the agreed upon timeline for submission is attached.

We are also in receipt of EPA's minutes, which is substantially similar to that of Syngenta's. However, the enclosed minutes are more detailed and addresses the questions posed by the Agency, and Syngenta's replies during the teleconference. Also, in one important aspect - the rationale for the meeting - the records indicate that EPA's DCI was driven by generic concerns over inhalation exposure/risk for all pesticides, not just for emamectin benzoate. The Agency indicated that it has made a determination that generic inhalation exposure to pesticides and their associated risk cannot always be properly determined by route - to - route extrapolations, especially from oral studies.

Our minutes also contain updates from the teleconference with respect to plasma half-life data and the associated MRID reference. It is more detailed regarding question - and - answer exchanges during the teleconference, including a planned consultation with OREB regarding dosing durations for mouse nose-only exposures.

Therefore, if agreeable, we would like a confirmation from the Agency that this document serves as the official record of the meeting due to its detail and accuracy. We appreciate your consideration of this proposal.

If you have any questions or comments about the conference call summary or this proposal, please contact me. I can be reached at (336) 632-2838

Sincerely yours,



Carolyn F. Brinkley
Sr. Regulatory Product Manager
Regulatory Affairs

Enclosures: Conference Call Summary

Record of Teleconference Meeting Between Syngenta and EPA to Discuss Study Guidance for Emamectin Benzoate Repeat Exposure Inhalation Study

| | |
|------------------------|--|
| Date & Time | Thursday August 4, 2005, 11:15 am – 12:15 pm (US, Eastern Standard Time) |
| Topic | To discuss, and to seek clarifications from EPA, on detailed procedures to follow in the conduct of the proposed 28-day repeat exposure inhalation study with emamectin benzoate in CF-1 mouse |
| Participants | <p>EPA: Tom Harris – Registration Division Paula Deschamp – Health Effects Division, Branch Chief Kathleen Raffaele – Toxicologist, IIED Elissa Reaves – Toxicologist, IIED</p> <p>Syngenta: Paul Hext – Toxicology, Syngenta Central Toxicology Laboratory (CTL), UK Patrick Rose – Toxicology, CTL, UK Tim Pastoor – Human Safety/Toxicology Greensboro Amechi Chukwudebe – Human Safety/Toxicology Greensboro Carolyn Brinkley – Regulatory Affairs, Greensboro</p> |
| Purpose | <p>The EPA requested a 28-day repeat exposure inhalation study with emamectin benzoate in CF-1 mice. The primary purpose of this meeting was threefold:</p> <ul style="list-style-type: none">• Syngenta to seek clarification from the Agency regarding the basis for this study request• Syngenta to seek clarification from the Agency regarding the basis for this study request in CF-1 mouse, since the standard guideline is based on rat• Syngenta to propose specific study details and ask for the Agency's feedback in order to agree on the study design. |
| Discussions | <p>Following introductions, the following points were discussed and the Agency's respective positions were conveyed to Syngenta.</p> <p>Item 1. Basis for Repeat Exposure Inhalation Study Request</p> <p>EPA issued this DCI based on the following factors: Generic concerns over general inhalation exposure for all pesticides, not just for emamectin benzoate. However, exposure via inhalation is significant for emamectin and the neurotoxicity of emamectin is a concern to the EPA. The Agency's determination that generic inhalation exposure to pesticides cannot always be properly determined by route – to – route extrapolations. In the past the EPA has used the oral study to determine potential short-term and medium term inhalation risk. However, the EPA is concerned that the oral study may not be appropriate for determining inhalation risk because the inhalation portal of entry could result in greater toxicity than the oral portal.</p> <p>Item 2. Basis for Selection of CF-1 Mouse as Test Species</p> <p>The EPA decided that the CF-1 mouse, not the rat, should be the test species for this DCI because the toxicity endpoint that the EPA is using for emamectin is based on studies with the CF-1 mouse.</p> |

Discussions (Cont'd) Item 3. Specific technical details proposed by Syngenta for the conduct of the repeat exposure inhalation study, and EPA's response

Syngenta's Technical Proposal Number 1 (test species). Syngenta will conduct this inhalation study, via nose-only exposure, using the standard CF-1 BR mouse from Charles River Laboratories

EPA Position: Conduct of this inhalation study, via nose-only exposure, and using the standard CF-1 mouse from Charles River Laboratories is acceptable

Syngenta's Technical Proposal Number 2 (number of test animals to use in study). In this study, EPA's standard guideline will be largely followed. However, CTL (in UK) usually conducts studies of this duration according to the relevant OECD guideline. The OECD guideline is similar to EPA's in many respects, except that the number of animals recommended, 5/sex/group, differs from that recommended by the EPA (10/sex/group). For this inhalation study, is 5/sex/group acceptable to the Agency?

EPA Position: The Agency feels very strongly that it can be very difficult to properly interpret a study with small group sizes of the order of 5/sex/group. To obtain valid results that can be properly interpreted, the Agency continues to insist on the EPA's standard recommended group size of 10 animals per sex per group.

Syngenta's Technical Proposal Number 3 (route and duration of exposure). According to EPA's guideline for this type of study, the test species is the rat. EPA is requiring this study with emamectin in the CF-1 mouse. Based on experience with studies in the rat and mouse, Syngenta believes that continuous nose-only exposure to the mice for 6 hours/day on a 5-day/week basis (per EPA based guideline) will be physiologically stressful since the mouse is less able to tolerate restraint in tubes. This could compromise the objectives of the study. Syngenta believes that 2 continuous exposures (one in the AM and one in the PM) for 2 hours each, with a recovery period in between will not be as stressful and, considering the relatively long plasma $t_{1/2}$ for emamectin benzoate (24 – 30 h) this exposure regimen should be sufficient to determine inhalation hazard and to assess inhalation risk. The risk assessment process can accommodate both exposure concentration and duration of exposure to calculate a total daily exposure. Will such inhalation exposure duration be acceptable to the EPA?

The Agency posed the following questions/suggestions:

1. Does Syngenta have any literature data to support the position that 6-hour daily exposures to mice will be highly stressful?

Syngenta's Response: Our rationale is largely based on CTL's and other laboratories' experience in conducting nose-only inhalation studies in mice where one of the major problems is the generation of unacceptably high body temperatures while animals are restrained in tubes.

2. Has Syngenta considered overcoming this stress situation by conducting whole body exposures instead?

Syngenta's Response: Because animals self groom, extensive oral exposure is possible. This could affect interpretation of the inhalation study results.

Discussions (Cont'd)

3. Is Syngenta aware of, or can Syngenta provide examples of regulatory studies with such reduced nose-only exposure periods?

Syngenta's Response: In studies conducted for the pharmaceutical industry, such reduced exposure periods are not unusual.

EPA's Position: In the absence of evidence to the contrary, EPA still considers a 6-hour continuous daily exposure necessary for study results to represent worker exposure in the field. Since the purpose of this study is to address potential inhalation risk to workers HFD representatives agreed to discuss the proposal with colleagues in the Occupational & Residential Exposure Branch (OREB).

Syngenta will provide further information on the stress-related issues with mice.

However, since Syngenta proposes to conduct preliminary acute and 5-day inhalation studies prior to the main study, the exposure period issue could be addressed again in a future teleconference, depending on the outcome of these preliminary studies, the availability of supporting literature, and the opinion of OREB experts.

Specific Suggestions from EPA

In keeping with Syngenta's stated desire at the outset to perform a valid study that will meet with EPA approval, the Agency suggested the following additional parameters to aid in study interpretation – even though these are not part of the standard repeat exposure inhalation study guideline.

1. Conduct histopathological examination of the nose and other inhalation entry portals.
2. For better and more interpretable histopathological examinations data, Syngenta should consider perfusion fixation of nervous tissues.
3. In addition to motor activity measurements specified in current study guideline, Syngenta should also consider measurements of behavioral endpoints.
4. Submit the study protocol to the Agency for review before study initiation.

Syngenta commented that histopathological examination of the entire respiratory tract (nasal passages, larynx, trachea and lungs) is conducted routinely in all repeat-exposure inhalation studies.

Syngenta agreed to consider the other requested parameters and also to examine various daily exposure duration regimens (e.g. 2 x 2 hours vs. 2 x 3 hours) as part of preliminary studies. Their inclusion in the main study will depend on preliminary study results and on the outcome of a subsequent teleconference with the Agency later in the year.

After the next teleconference, Syngenta will submit a protocol for Agency review prior to initiation of the main study.

**Conclusions and
Follow-up Actions**

1. Syngenta will conduct the proposed 28-day repeat exposure inhalation study using the standard CF-1 mice from Charles River Laboratories.
2. The number of test animals used in the main study will be 10/sex/group.
3. Unless literature data, OREB opinions or results from preliminary studies indicate otherwise, EPA wants daily exposure duration of 3 x 2 hours in the study. The agency agreed to provide this feedback prior to Syngenta initiating the preliminary study. Syngenta agreed to document the rationale for reduced exposure in mice (with supporting literature if available) and e-mail to EPA.
4. At EPA's request, and to aid in decision regarding exposure duration, Syngenta agreed to provide the Agency with the citation for the regulatory study (previously submitted to EPA) where the plasma half-life of emamectin benzoate was determined to be greater than 24 hours.

UPDATE: The half-life reference is as follows:

MRID Number: 42851523. Study Title: *The Tissue Distribution, Metabolism, and Excretion of [¹⁴C]-4"-Deoxy-4"-epimethylamino Avermectin B1a (MAB1a) Benzoate in Rats. ARM-6.* Date Submitted to EPA: June 30, 1993.

Summary: Principal route of elimination is via feces (94-104% of total administered dose independent of sex or route of administration). The plasma _{0.5} following single *per os* or intravenous exposures range from 29 – 51 hours for male and female rats.

| Sex | Half-life (hr; iv) | Half-life (hr; po) |
|--------|--------------------|--------------------|
| Male | 29 | 34 |
| Female | 41 | 51 |

5. At the conclusion of the preliminary inhalation studies, Syngenta will arrange another teleconference with the EPA to discuss the final outlines for the main study. This will be followed by the main study protocol, which will be provided to the Agency for review and comments.
6. The milestones and associated timelines summarized below were proposed by Syngenta and were acceptable to the EPA.

| Milestones | Approx Start Date | Approx End Date |
|--|--------------------|-------------------|
| Preliminary studies | September 15, 2005 | November 30, 2005 |
| Teleconference with EPA | December 12, 2005 | |
| 28-day Inhalation Study Protocol to EPA for Review | January 9, 2006 | |
| 28-day Inhalation Study | January 23, 2006 | June – July 2006 |

Based on these timelines, Syngenta expects to have the final report for this 28-day repeat exposure inhalation study at the EPA by August 1, 2006.

MEETING NOTES

topic:

emamectin -

28-day inhalation

| | | | |
|------------|--|-----------|-----------------|
| date: | 8/4/05 | location: | phone conf call |
| attendees: | Syngenta: Carolyn Brinkley, Amechi Chukwudebe, Paul Hext, Tim Pastoor, Patrick Rose EPA: Paula Deschamp, Nancy Dodd, Tom Harris, Kathleen Raffaele, Elissa Reaves | | |
| purpose: | discuss protocol for 28-day inhalation study for emamectin | | |

ACTION ITEMS:

- *Syn send email (TH, cc PD) w/ question and background info regarding split 2 x 2 application; include MRID for half-life
- *EPA respond to question about split application, after receiving information from Syngenta
- *both submit/review draft protocols for preliminary study and final study (see below for timing)

NEXT MEETING:

NOTES:

Background

- Why is 28-day inhalation required? This is a significant route of exposure but we don't have any data other than acute study.
- Why use CF-1 mouse? This strain is more sensitive to the 'mectins, and is currently the animal model used in the studies selected for regulatory endpoints for emamectin. Results from 28-day inhalation will be easier to compare with other tox data, and it is appropriate to use the most sensitive species for regulatory purposes. Use the standard (heterozygous) strain.

Protocol

- * Syngenta should submit protocol for any studies for EPA approval before starting study.
- General concept is to use EPA protocol for 90-day inhalation but only conduct for 28 days.
- Be sure to do FOB, motor activity, etc specified in EPA protocol.
- Also do point of entry (nose) histopathology and do perfusion fixation for neurological tissues.
- Number of mice: do EPA required 10, not OECD 5.
- Stress:
 - Syngenta stated that 6-hour head only is stressful on mice; max is 2 hours at a time. They suggested doing 2 exposures of 2 hours each per day. Half-life of emamectin is 24-30 hours so gap should not significantly reduce exposure.
 - EPA suggested that IF we accept split exposure that Syngenta do 3 exposures of 2 hours each per day (as this would be most comparable to the 6 h exposure period specified

- inhalation guideline).
- Syngenta stated that whole body exposure would overestimate effect by 5x due to oral ingestion from body grooming.
- * Syngenta send email ASAP (to Tom Harris, cc Paula Deschamp since TH out next week) restating this issue and their arguments. Include MRID of half-life study.
- * EPA discuss the split exposure proposal and get back to Syngenta with decision ASAP.

Schedule

| | |
|-------------|---|
| early Sept | * Syngenta email protocol for preliminary study |
| mid Sept | * EPA respond to preliminary study protocol |
| late Sept | * Syngenta conduct preliminary studies (2 & 5 day) |
| Oct | * Syngenta submit draft of final protocol |
| early Nov | * Syngenta submit results of preliminary histopathology |
| Nov | * EPA complete review of final protocol |
| Jan | * Syngenta start final study |
| summer 2006 | * Syngenta submit results of final study |



U.S. ENVIRONMENTAL PROTECTION AGENCY
Office of Pesticide Programs
Registration Division (7505C)
1200 Pennsylvania Ave., NW
Washington, D.C. 20460

EPA Reg. Number:

100-902

Date of

2/10/05

Term of Issuance:

Conditional, extended until
5/1/06

Name of Pesticide Product:

Eamectin Benzoate
Technical

NOTICE OF PESTICIDE:

☒ Registration
☐ Reregistration

(under FIFRA, as amended)

Name and Address of Registrant (include ZIP Code):

Carolyn Brinkley
Syngenta Crop Protection, Inc.
PO Box 18300
Greensboro, NC 27419

Note: Changes in labeling differing in substance from that accepted in connection with this registration must be submitted to and accepted by the Registration Division prior to use of the label in commerce. In any correspondence on this product always refer to the above EPA registration number.

On the basis of information furnished by the registrant, the above named pesticide is hereby registered/reregistered under the Federal Insecticide, Fungicide and Rodenticide Act.

Registration is in no way to be construed as an endorsement or recommendation of this product by the Agency. In order to protect health and the environment, the Administrator, on his motion, may at any time suspend or cancel the registration of a pesticide in accordance with the Act. The acceptance of any name in connection with the registration of a product under this Act is not to be construed as giving the registrant a right to exclusive use of the name or to its use if it has been covered by others.

The above product was conditionally registered on 5/19/99 with an expiration date of 5/1/02. The registration was extended on 4/19/02 by EPA until 5/1/03, on 4/18/03 until 5/1/04, and on 3/30/04 until 5/1/05. This letter serves to extend the conditional registration expiration date for this product an additional year, i.e. until 5/1/06.

This time extension will allow for review of an estuarine/marine invertebrate life-cycle study (guideline OPP 72-4b = OPPTS 850.1350) which was noted as a condition of registration for end use products EPA Registration # 100-903 and # 100-904. After the EPA denial of a Syngenta waiver request the registrant agreed to run the study. The study was submitted on 1/7/03, assigned MRID 458330-01, and is currently in review.

Signature of Approving Official:

Thomas C. Harris, Biologist
Insecticide-Rodenticide Branch
Registration Division (7504C)

Date:

2/10/05



U.S. ENVIRONMENTAL PROTECTION AGENCY
Office of Pesticide Programs
Registration Division (7505C)
1200 Pennsylvania Ave., NW
Washington, D.C. 20460

EPA Reg. Number:

100-902

Date of

3/30/04

NOTICE OF PESTICIDE:

☒ Registration

(under FIFRA, as amended)

☐ Reregistration

Term of Issuance:

Conditional, extended until
5/1/05

Name of Pesticide Product:

Emamectin Benzoate
Technical

Name and Address of Registrant (include ZIP Code):

Carolyn Brinkley
Syngenta Crop Protection, Inc.
PO Box 18300
Greensboro, NC 27419

Note: Changes in labeling differing in substance from that accepted in connection with this registration must be submitted to and accepted by the Registration Division prior to use of the label in commerce. In any correspondence on this product always refer to the above EPA registration number.

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Signature of Approving Official:

Thomas C. Harris, Biologist
Insecticide-Rodenticide Branch
Registration Division (7504C)

Date:

3/30/04



"Sherman, Gary"
<GSherman@CVM.FDA.GOV
>

12/01/2004 12:03 PM

To: Thomas Harris/DC/USEPA/US@EPA
cc: "Mulligan, Louis T" <LMULLIGA@CVM.FDA.GOV>

bcc

Subject: Emamectin (Slice)

Dear Tom,

Thank you for your follow-up call about the status of the Emamectin file. I do sincerely apologize for how slow the wheels have turned on this issue, and I very much appreciate your considerable patience! May I ask you to hold the file/review for just a while longer? We believe we will soon have this matter resolved such that the two companies in question (SPAH and Syngenta) will communicate directly, with Syngenta directly providing to SPAH a copy of the EPA review document in question. This would mean we (FDA) would not have to obtain a copy of the review from you. While I anticipate this will all transpire as planned, I do not want to have you re-file into your archives the documents you've already fished out for us once, only to find out that the two companies did not or could not follow through, and once again want to try to provide your office and ours with the appropriate right-of-access letters in order to effect the document exchange as originally envisioned. I can promise you that once I have the official SPAH submission in hand, and I know whether we actually have what we need, I'll contact you immediately so we can put this to bed once and for all. I do not expect this will take long. By January of 2005 I should be able to let you know how we can proceed to close out this issue, assuming that by then SPAH and Syngenta will have effectively communicated, and we at FDA have received a complete submission from SPAH. I am optimistic about a relatively expeditious turn-around on this because SPAH is anxious to move forward with review of this product. Will this approach I've proposed work at your end or do you have some other suggestion. I'm open to any ideas you may have.

Thanks again for your patience through all this, and I hope you have a wonderful winter holiday.

Gary

Gary B. Sherman, MS, DVM, PhD
gsherman@cvm.fda.gov
Direct 301-827-0122; Fax 301-594-2298
Division of Human Food Safety, HFV-153
Center for Veterinary Medicine
US Food & Drug Administration
7500 Standish Place
Rockville, Maryland 20855-2746 USA

The opinions and information in this message are those of the author and do not necessarily reflect the views and policies of the U.S. Food and Drug Administration. Because of the nature of electronically transferred information, the integrity or security of this message cannot be guaranteed.



Carolyn F. Brinkley
Sr. Regulatory Product Manager
Regulatory Affairs
carolyn.brinkley@syngenta.com
(336) 632 2838

Syngenta Crop Protection, Inc.
P. O. Box 18300
410 Swing Road
Greensboro, NC 27419-8300

September 16, 2004

Mr. Thomas Harris
Insecticide-Rodenticide Branch
U.S. Environmental Protection Agency
Office of Pesticide Programs
Ariel Rios Building
1200 Pennsylvania Ave, NW
Washington, DC 20460-0001

**SUBJECT: EMAMECTIN BENZOATE TECHNICAL
EPA REG. NO. 100-902
REVISED AUTHORIZATION FOR EPA-FDA DISCUSSION OF
SPECIFIED TWO-GENERATION REPRODUCTION STUDY**

Dear Mr. Harris:

Syngenta Crop Protection, Inc. herewith authorizes toxicologists with the Office of Pesticide Programs Health Effects Division the Environmental Protection Agency to discuss the cited study below¹, the EPA's 1994 review of that study (copy attached), and the data from this study that supported the conclusions in this review, with FDA toxicologists. This authorization is limited to a discussion of this study and the EPA's review of the study data² solely with respect to Schering-Plough Animal Health's application for FDA approval of an emamectin -based product known as Slice™ (emamectin benzoate 0.2% Type A medicated article for salmon), INAD 010-418). Slice™ is proposed for use in the feed of farm-raised fish primarily for the control of sea lice.

¹ EPA MRID No.
42851511

CITATION

Lankas, G. (1993) MK-0244: Two-Generation Dietary Reproduction Study in Rats: Lab Project Number: 618-244-TOX49: TT #91-715-0: AS-3446. Unpublished study prepared by Merck Research Labs.

² Data Evaluation Report MK-0244.

Study Type: Reproductive Toxicity. Prepared for: Health Effects Division, Office of Pesticide Programs, US Environmental Protection Agency, 1921 Jefferson Davis Highway; Arlington, VA 22031

Prepared by: Clement International Corporation, 9300 Lee Highway; Fairfax, VA 22031

Principal Reviewer: Sanju Diwan, Ph.D. Date: 5/16/94

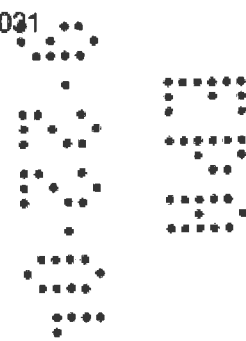
Independent Reviewer: Pia Lindstrom, D.P.H. Date 5/16/94

QA/QC Manager: Cort A. Maczke, Ph.D. Date: 5/16/94

Contract Number: 68D10075

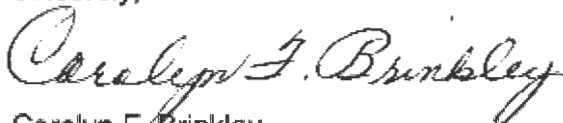
Work Assignment Number: 3-25

Clement Number: 84



This authorization is qualified to the extent, however, that: (1) Schering-Plough Animal Health or any other person except the Administrator shall not have access to or said referenced data, and/or EPA MRID number unless specifically authorized in writing by Syngenta Crop Protection, Inc. (2) this authorization shall not be construed as authorization for the EPA to discuss with the FDA any Syngenta data, directly or indirectly, in support of any subsequent application submitted by the applicant to the FDA or the EPA including, without limitation, applications for new registration or amended registration. and (3) this authorization shall not be transferred by the applicant in any manner whatsoever without express prior written consent of Syngenta.

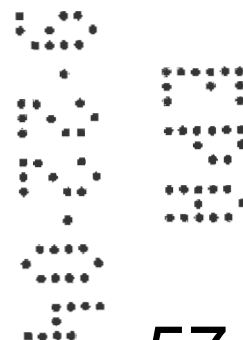
Sincerely,



Carolyn F. Brinkley
Sr. Regulatory Product Manager
Regulatory Affairs

Enclosure: Data Evaluation Report MK-0244; Study Type: Reproductive
Toxicity; Dated 5/16/94

cc: Dr. Louis T. Mulligan
Team Leader - Toxicology Team
Division of Human Food Safety (HFV-150)
C/O Document Control Unit (HFV-199)
Center for Veterinary Medicine
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855



bcc: G. Peters
S. Reasons
C. Moseley
C. Biggers
Trina Brodie/Customer Service File – Schering-Plough

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FINAL

DATA EVALUATION REPORT

MK-0244

Study Type: Reproductive Toxicity

Prepared for:

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031

Principal Reviewer

Walter L. McLain for
Sanju Diwan, Ph.D.

Date 5/16/94

Independent Reviewer

Pia Lindström
Pia Lindström, D.P.H.

Date 5/16/94

QA/QC Manager

Sharon Segal, Ph.D.
Carol A. Maczka, Ph.D.

Date 5/16/94

Contract Number: 68D10075
Work Assignment Number: 3-25
Clement Number: 84
Project Officer: Caroline Gordon

59

Guideline Series 83-4: Reproductive Toxicity

EPA Reviewer: Myron Ottley, Ph.D.
Review Section IV, Toxicology Branch I/HED

Signature: M. Ottley
Date: 8/29/94

EPA Section Head: Marion Copley, D.V.M.
Review Section IV, Toxicology Branch I/HED

Signature: Marion Copley
Date: 9/21/94

DATA EVALUATION REPORT

STUDY TYPE: Reproductive Toxicity - Rat (Guideline Series 83-4)

NRID NO.: 428515-11

TOX CHEM. NO.: New chemical

TEST MATERIAL: 4"-Deoxy-4"-epi-methylamino-avermectin B1 (benzoate salt)

SYNONYM: MK-0244; Deoxy avermectin

STUDY NUMBER: TT #91-715-0

SPONSOR: Agricultural Research and Development, Merck and Company Inc., Three Bridges, NJ

TESTING FACILITY: Merck Research Laboratories, Merck and Company Inc., West Point, PA

TITLE OF REPORT: MK-0244: Two-Generation Dietary Reproduction Study in Rats

AUTHOR: G.R. Lankas

DATE REPORT ISSUED: May 12, 1993

CONCLUSIONS:

Dose levels: Administered to Sprague-Dawley rats in the diet, 0, 0.1, 0.6, or 3.6/1.8 mg/kg/day for two generations

Systemic NOEL: 0.6 mg/kg/day

Systemic LOEL: 1.8 mg/kg/day, based on decreased body weight gain and histopathological changes (neuronal degeneration in the brain and spinal cord) in both sexes and generations

Reproductive NOEL: 0.6 mg/kg/day

Reproductive LOEL: 1.8 mg/kg/day based on decreased fecundity and fertility indices and clinical signs (tremors and hind limb extension) in offspring of both generations

Classification: Core Guideline Data

This study satisfies the guideline requirements for a reproductive toxicity study (83-4) in rats.

A. MATERIALS**Test Compound**

Purity: >96%
Description: None
Lot number: L-656,748-052S002
Date received: Not reported
Contaminants: Not reported
Storage: Ambient temperature

Test Animals

Species: Rat
Strain: Sprague-Dawley [CrI:CD® (SD) BR]
Source: Charles River Laboratories, Raleigh, NC (females) and Kingston, NY (males)
Age: Approximately 63 days on study day 0
Weight: F₀ males--292-405 g on study day 0
F₀ females--179-273 g on study day 0

B. STUDY DESIGN

This study was designed to assess the effects of MK-0244 on the growth and reproductive performance of rats during two successive generations.

Mating Procedure

After approximately 3 weeks of acclimatization followed by 9 weeks of dietary treatment, F₀ females were mated with males from the same group in a ratio of 1:1 for a maximum of 21 days until a copulatory plug was detected or sperm were observed in a vaginal smear. The F₀ generation was mated for a second time approximately 3 weeks following the weaning of the F_{1a} pups. Nonmated animals were paired with fertile animals of the opposite sex from each group for a maximum of 21 days. The day on which mating was confirmed was considered gestational day (GD) 0. F₁ animals were mated in a similar manner avoiding sibling matings.

Animal Husbandry

Rodent diet (Purina Certified Rodent Chow #5002M) and tap water were available ad libitum. The temperature was maintained at 20°-27°C; humidity data were not reported. A 12-hour light/dark cycle was maintained. The study author did not report the number of air changes/hour.

Group Arrangement

F₀ animals were distributed using a randomization procedure based on body weight. The groups were as follows:

| Test Group | Dosage Level (mg/kg/day) | Number of Animals Assigned per Group | | | |
|------------|-----------------------------|--------------------------------------|---------|----------------|---------|
| | | F ₀ | | F ₁ | |
| | | Males | Females | Males | Females |
| Control | 0 | 33 | 33 | 33 | 33 |
| Low dose | 0.1 | 33 | 33 | 33 | 33 |
| Mid dose | 0.6 | 33 | 33 | 33 | 33 |
| High dose* | 3.6 | 33 | 33 | 33 | 33 |

*The high-dosage level received by the F₀ and F_{1a} females was reduced to 1.8 mg/kg/day on GD 0 following the second cohabitation of F₀ females.

Dosage Administered

Test diets were prepared once or twice weekly by diluting a concentrated premix with untreated diet to achieve appropriate concentrations. Dosages were adjusted to maintain the desired concentration. Diets were stored at room temperature until used. Analyses for concentration, homogeneity, and stability were conducted during weeks 1 and 3 for the F₀ generation and week 7 for the F_{1a} generation.

Dosage Rationale

Dosages were selected based upon the results of a one-generation range-finding reproduction study (TT #90-724-9; MRID No. 427436-33; see Attachment I for a detailed description of the study). Sprague-Dawley female rats (12 dams/group) were administered MK-0243 either by gavage or in the diet on gestational day (GD) 0 through lactational day (LD) 21. The dose levels for the gavage study were 0, 0.1, 0.7, or 5 mg/kg/day, while the diet levels were 0, 1, 7, or 50 ppm (approximately 0, 0.1, 0.7, or 4.6 mg/kg/day).

Maternal toxicity, observed at 5 mg/kg/day in the gavage study and at 50 ppm in the diet study, was manifested as significantly decreased body weight gain on GDs 8-16 for both studies, on LDs 0-8 in the gavage study, and on LDs 8-12 in the diet study. These effects were more pronounced in the gavage study particularly during the first part of the lactation period. Food consumption was also affected more severely in the gavage study during the lactation period. Reproductive toxicity, observed at 5 mg/kg/day in the gavage study and at 50 ppm in the diet study, was manifested as excessive pup mortality during lactation in the gavage study. Also, surviving pups in both studies experienced decreased body weight and tremors during lactation. Histopathology of brain and spinal cord tissues at 50 ppm demonstrated degeneration of these tissues.

Gavage Study: Maternal NOEL = 0.7 mg/kg/day; maternal LOEL = 5 mg/kg/day (decreased body weight gain and food consumption); reproductive NOEL = 0.7 mg/kg/day; reproductive LOEL = 5 mg/kg/day (excessive pup mortality, decreased pup body weight, and increased clinical signs in pups)

Diet Study: Maternal NOEL = 7 ppm (0.7 mg/kg/day); maternal LOEL = 50 ppm (4.6 mg/kg/day) (decreased body weight gain and food consumption); reproductive NOEL = 7 ppm (0.7 mg/kg/day); reproductive LOEL = 50 ppm (4.6 mg/kg/day) (decreased pup body weight, increased clinical signs [tremors], and histopathological signs [brain and spinal cord degeneration])

Observations

Observations were made once daily for mortality and physical signs. Body weight data were recorded weekly during premating. Body weight data for females were also recorded on GDs 0, 4, 8, 12, 16, 20, and 24 and on lactational days (LDs) 0, 4, 8, 12, 16, 20, and 21; females without live pups were weighed once weekly until sacrifice. Food consumption data were recorded over a 6-day interval during premating; for females it was also recorded over a 4-day interval during GDs and LDs 0-20.

The following data were recorded for each litter:

- Number of live and dead pups, sex, and individual pup weight on LDs 0, 4, 7, 14, and 21
- External anomalies on LDs 0, 4, and 21
- Mortality and physical signs once daily

On day 4, pups were randomly culled to four/sex/litter whenever possible. Pups that died during lactation and 10 pups/sex/litter (randomly selected) were subjected to gross necropsy. Culled pups were examined externally and discarded. Dead pups were fixed in 10% buffered formalin and examined for visceral abnormalities. Twenty-five male and 25 female F_{1a} pups were randomly selected as F_1 parental animals.

Parental males were sacrificed and necropsied at the time of parturition. Parental females were sacrificed and necropsied after weaning of their respective litters between LD 22 and 28. After gross examination, the following tissues were preserved in 10% buffered formalin and processed for histological examination from animals in the control and high-dosage groups.

- | | |
|-----------------|--------------------|
| - Brain | - Ovaries |
| - Spinal cord | - Testes |
| - Sciatic nerve | - Epididymides |
| - Uterus | - Seminal vesicles |
| - Vagina | - Prostate |
| - Gross lesions | |

In addition, brain, spinal cord, and sciatic nerve tissues from animals in the 0.6-mg/kg/day group and the sciatic nerve tissue from animals in the 0.1-mg/kg/day group were processed for histopathological examination.

Statistical Analysis

The following analyses were conducted:

- Parental and pup body weight/weight gain; food consumption; length of gestation; time to mating; mating, fertility, and fecundity indices; and numbers of implantation sites and live and dead pups-- Analysis of variance or covariance followed by a trend test and rankit transformation (for continuous variables) or Mantel-Haenszel test (for discrete variables)
- Infertility--NOSTASOT, Mantel-Haenszel test, and/or Chi-Square test

Compliance

The following statements were provided:

- A signed Statement of No Data Confidentiality Claims, dated June 3, 1993
- A signed Statement of Compliance with EPA GLPs dated May 5, and June 2 and 3, 1993
- A signed Quality Assurance Statement, dated May 5, 1993

C. RESULTS

Test Material Analysis

Results of concentration analyses for two separate batches revealed values ranging from 82% to 106% of target (with two exceptions) for all three dosage levels. Homogeneity, also analyzed at all dosage levels on three separate batches, revealed values ranging from 82% to 108% of target. The results of stability analyses revealed values ranging from 80% to 100%.

Parental Toxicity

Mortality

No compound-related mortalities were observed at any exposure level in either sex or generation. In the F_0 generation, three males were found dead (one each at 0.1, 0.6, and 3.6 mg/kg/day during weeks 18, 7, and 20, respectively). Four F_0 females were found dead (one at 0.1 mg/kg/day, one at 0.6 mg/kg/day, and two at 3.6/1.8 mg/kg/day during weeks 21, 15, and 22-24, respectively). No treatment-related gross findings were observed at necropsy.

In the F_1 generation, three males were sacrificed moribund (one each at 0, 0.1, and 3.6 mg/kg/day during weeks 13, 13 and 12, respectively); necropsy did not reveal the cause of death. Among F_1 females, one animal from the control group was found dead at week 19. In addition, four animals were sacrificed moribund (one at 0.1 mg/kg/day, two at 0.6 mg/kg/day, and one at 3.6/1.8 mg/kg/day during weeks 19, 2, and 1, respectively). No treatment-related gross findings were observed at necropsy.

Clinical Observations

No compound-related clinical signs were observed at any exposure level in either sex or generation.

Body Weight

Compound-related effects in body weight gain were observed at 3.6/1.8 mg/kg/day for both sexes and generations. Summaries of body weight/weight gain data for selected intervals are presented in Tables 1 and 2. Detailed results are discussed below.

In the F_0 generation among males, a significantly decreasing trend with increasing dosage was observed with regard to body weight gain (Table 1) for the entire premating period (weeks -1 to 8). Body weights in these males (data not shown) decreased slightly at 3.6 mg/kg/day throughout the same period. For F_0 females during the premating period, a significantly increasing trend with increasing dosage was observed with regard to body weight gain (Table 1), while body weights increased slightly above control (data not shown). During the first gestation period, a significantly decreasing trend with increasing dosage was observed with regard to body weight gain (Table 2). Body weight during the first gestation period (data not shown) was comparable among all dose groups. No treatment-related effects on body weight or weight gain were seen during the second gestation period and first and second lactation periods (data not shown).

In the F_1 generation among males, a significantly decreasing trend with increasing dosage was observed with regard to body weight gain (Table 1) for the entire premating period (weeks -1 to 15). Body weight in these males decreased below control throughout the study at 3.6 mg/kg/day (data not shown). For F_1 females during the premating period, a significantly decreasing trend with increasing dosage was also observed with regard to body weight gain (Table 1), while body weight decreased below control at 1.8 mg/kg/day. During the gestation period, a significantly decreasing trend with increasing dosage was observed with regard to body weight gain (Table 2) on GDs 0-20, while body weight (data not shown) was consistently lower than control. No treatment-related effects on body weight or weight gain were seen during lactation (data not shown).

Food Consumption

No compound-related effects on food consumption (g/animal/day) were observed in either sex or generation. For F_0 lactating females, a decrease in food consumption was noted at 3.6/1.8 mg/kg/day on LDs 4, 8, and 12, and at all three dosage levels on LDs 16 and 20. These decreases were not seen for F_1 females, and therefore, they were considered to be incidental.

Histopathology

Compound-related effects in histopathology were observed in both sexes and generations at 3.6/1.8 mg/kg/day. In the F_0 generation, neuronal degeneration in the brain and/or spinal cord was observed in males (29/33 and 31/33, respectively) and females (23/33 and 5/33, respectively); slight degeneration of the sciatic nerve was observed in 4 of 33 males.

In the F_1 generation, neuronal degeneration in the brain and/or spinal cord was also noted in males (23/25 and 23/25, respectively) and females (18/27 and 7/27, respectively); no degeneration of sciatic nerves was observed in males at 3.6/1.8 mg/kg/day.

Reproductive Toxicity

Compound-related reproductive effects were observed at 3.6/1.8 mg/kg/day in both generations. Summaries of reproductive parameters are presented in Tables 3, 4, 5 and 6. Detailed results are discussed below.

In the F_0 generation (Table 3) during the first mating period, nonsignificant decreases in the fertility index were observed at 0.1, 0.6, and 3.6 mg/kg/day as a result of decreases in the fecundity index. During the second mating period in the F_0 generation (Table 4) and in the F_1 generation (Table 5), similar decreases in fecundity and fertility indices were observed only at 3.6/1.8 mg/kg/day.

In the F_0 generation (Table 3), a significant trend towards decreasing number of live pups/litter with increasing dosage was observed for the first mating. However, all incidents were within the range of historical controls, and therefore, this finding was considered to be incidental. In addition, similar trends were not seen in the F_0 second mating and F_1 mating.

In F_{1a} and F_{1b} litters (Table 6) prior to weaning, the following clinical signs were observed at 3.6/1.8 mg/kg/day: intermittent head tremors and/or whole body tremors, hind limb extension and its limited use, and/or hind limb splay. Some signs in F_{1a} pups (hind limb splay in 25/25 males and 27/27 females and whole body tremors in 10/25 males and 13/27 females) persisted during the post-weaning period (data not shown). In F_2 litters (Table 6), on the contrary, only 1 of 11 litters at 3.6/1.8 mg/kg/day exhibited clinical signs consisting of whole body tremors and hind limb extension from LD 14 to LD 21. Thus, lowering the high-dosage level from 3.6 to 1.8 mg/kg/day beginning on GD 0 reduced the incidence of treatment-related signs in F_{1b} and F_2 pups.

Among F_{1a} pups (Table 3), a significantly decreasing trend with increasing dosage was observed on body weight for both sexes on LDs 14 and 21. For F_2 offspring (Table 5), a significantly decreasing trend with increasing dosage was observed with regard to body weight for male pups on LD 4 and for male and female pups on LDs 14 and 21. The decreases in pup body weight during late lactation may have been associated with the physical inability of the pups to reach the feeder as a consequence of tremors and hind limb immobility.

D. REVIEWERS' DISCUSSION/CONCLUSIONS

Test Material Analyses

The purity, homogeneity, and stability of the test compound were confirmed. With the exception of a few occasions, the concentration analyses revealed values within $\pm 20\%$ of target.

Parental Toxicity

Compound-related parental toxicity was observed at 3.6/1.8 mg/kg/day. It was manifested as decreased body weight gain in F_0 and F_1 males and females during premating, and in F_0 and F_1 females during gestation. In addition, histopathological changes, including neuronal degeneration in the brain and spinal cord, were observed in both generations and sexes. Based on these results, the NOEL and LOEL for parental toxicity were 0.6 and 1.8 mg/kg/day, respectively.

Reproductive Toxicity

Compound-related reproductive toxicity was observed at 3.6/1.8 mg/kg/day. It was manifested in both generations as decreases in the fecundity and fertility indices. The number of infertile F_0 females increased at 1.8 mg/kg/day (21% versus 3% in the control) when animals that did not produce a pregnancy in the first mating were paired during the second mating with known fertile animals. The number of infertile males, however, was comparable across all groups. This observation suggests that the treatment specifically affected the females. Clinical signs of toxicity were seen in pups from both generations. Incidences of clinical signs decreased in F_2 litters receiving lower dosage levels (1.8 mg/kg/day). Based on these results, the NOEL and LOEL for reproductive toxicity were 0.6 and 1.8 mg/kg/day, respectively.

E. CORE CLASSIFICATION

Core Guideline Data. This study satisfies the guideline requirements for a reproductive toxicity study (83-4) in rats.

Systemic NOEL = 0.6 mg/kg/day

Systemic LOEL = 1.8 mg/kg/day based on decreased body weight gain and histopathological changes in neural tissue of both sexes and generations

Reproductive NOEL = 0.6 mg/kg/day

Reproductive LOEL = 1.8 mg/kg/day based on decreased fecundity and fertility and clinical signs in pups of both generations

F. RISK ASSESSMENT: Not applicable

TABLE 1. Body Weight and Weight Gain (g) During the Premating Period for Rats Exposed to MK-0244 for Two Successive Generations^{a, b}

| Week of Treatment | Exposure Level (mg/kg/day) | | | |
|------------------------------|----------------------------|-----|-----|----------------------|
| | 0 | 0.1 | 0.6 | 3.6/1.8 ^c |
| <u>F₀ males</u> | | | | |
| -1 | 350 | 348 | 347 | 346 |
| 1 | 393 | 388 | 389 | 392 |
| 4 | 501 | 493 | 495 | 494 |
| 8 | 583 | 576 | 583 | 565 |
| -1 to 8 | 233 | 227 | 235 | 219* |
| <u>F₀ females</u> | | | | |
| -1 | 230 | 229 | 228 | 232 |
| 1 | 243 | 244 | 244 | 244 |
| 4 | 288 | 291 | 289 | 293 |
| 8 | 317 | 323 | 322 | 332 |
| -1 to 8 | 87 | 95 | 93 | 101* |
| <u>F₁ males</u> | | | | |
| -1 | 82 | 81 | 81 | 59 |
| 1 | 134 | 132 | 133 | 100 |
| 4 | 324 | 316 | 317 | 261 |
| 8 | 496 | 489 | 492 | 437 |
| 12 | 571 | 570 | 579 | 508 |
| 14 | 606 | 599 | 608 | 545 |
| -1 to 14 | 536 | 530 | 542 | 500* |
| <u>F₁ females</u> | | | | |
| -1 | 85 | 87 | 86 | 67 |
| 1 | 130 | 136 | 133 | 108 |
| 4 | 227 | 231 | 230 | 200 |
| 8 | 295 | 295 | 298 | 262 |
| 12 | 326 | 325 | 330 | 297 |
| 14 | 342 | 338 | 347 | 316 |
| -1 to 14 | 257 | 254 | 261 | 249* |

^aData were extracted from Study No. TT 891-715-0, Tables A-8, A-9, A-46, and A-47.^bStandard deviations were not provided.^cThe high-dosage received by the F₀ and F_{1m} females was reduced to 1.8 mg/kg/day on GD 0 following the second cohabitation of F₀ females.

*Significant trend through indicated dosage (p<0.05)

TABLE 2. Body Weight Gain (g \pm S.D.) During Gestation for Rats Exposed to MK-0244 for Two Successive Generations^{a, b}

| Gestation Day | Exposure Level (mg/kg/day) | | | |
|---|----------------------------|-----|-----|----------------------|
| | 0 | 0.1 | 0.6 | 3.6/1.8 ^c |
| <u>F₀ generation-F₁ litters</u> | | | | |
| 0-12 | 59 | 62 | 61 | 61 |
| 12-16 | 20 | 19 | 16 | 11 |
| 16-20 | 63 | 63 | 64 | 63 |
| 0-20 | 142 | 144 | 142 | 136* |
| | | | | |
| <u>F₁ generation-F₂ litters</u> | | | | |
| 0-12 | 54 | 60 | 59 | 42 |
| 12-16 | 25 | 25 | 28 | 31 |
| 16-20 | 54 | 51 | 57 | 53 |
| 0-20 | 133 | 135 | 145 | 126* |

^aData were extracted from Study No. IT #91-715-0, Tables A-13 and A-51.

^bStandard deviations were not provided.

^cThe high-dosage received by the F₀ and F_{1a} females was reduced to 1.8 mg/kg/day on GD 0 following the second cohabitation of F₀ females.

*significant trend through indicated dosage (p<0.05)

TABLE 3. Effects of Exposure to MK-0244 on P₀ Reproductive Parameters and P_{1a} Offspring Survival and Body Weight^a

| Parameter | Observation at Each Exposure Level (mg/kg/day) | | | |
|--|--|-----------|-----------|------------|
| | 0 | 0.1 | 0.6 | 3.6 |
| No. paired females | 33 | 33 | 33 | 33 |
| No. matings | 33 | 31 | 33 | 31 |
| Mating index (%) ^{b,c} | 100 | 94 | 100 | 94 |
| No. pregnant females | 30 | 22 | 25 | 22 |
| Fertility index (%) ^d | 91 | 67 | 76 | 67 |
| Fecundity index (%) ^e | 91 | 71 | 76 | 71 |
| Gestation index (%) ^f | 100 | 100 | 100 | 100 |
| Gestation length (days) | 22.5 | 22.4 | 22.7 | 22.5 |
| No. females with liveborn pups | 30 | 22 | 25 | 22 |
| Total no. live pups | | | | |
| Day 0 | 424 | 331 | 367 | 287 |
| Day 4, precull ^h | 406 | 319 | 355 | 278 |
| Day 21 ^h | 228 | 173 | 191 | 161 |
| Mean no. live pups/litter ^g | | | | |
| Day 0 | 14.1 (30) | 15.0 (22) | 14.7 (25) | 13.0* (22) |
| Day 4, precull ^h | 13.5 (30) | 14.5 (22) | 14.2 (25) | 12.6 (22) |
| Day 21 ^h | 7.9 (29) | 7.9 (22) | 7.9 (24) | 7.6 (21) |
| Live birth index (%) ^{b,h} | 94 | 99 | 97 | 96 |
| Viability index (%) ^{b,i} | 96 | 96 | 97 | 97 |
| Lactation index (%) ^{b,j} | 99 | 99 | 99 | 99 |
| Mean pup body weight (g), males | | | | |
| Day 0 | 6.6 | 6.6 | 6.7 | 6.7 |
| Day 7 | 18.1 | 17.7 | 18.3 | 18.2 |
| Day 21 | 59.8 | 59.2 | 60.8 | 40.2* |
| Mean pup body weight (g), females | | | | |
| Day 0 | 6.3 | 6.3 | 6.4 | 6.4 |
| Day 7 | 17.2 | 17.5 | 17.3 | 17.4 |
| Day 21 | 56.9 | 57.8 | 58.9 | 40.4* |
| Sex ratio (% males day 0) ^b | 47 | 53 | 47 | 49 |

^aData were extracted from Study No. TT #91-715-0, Tables A-32, A-33, and A-98.^bCalculated (but not analyzed) by the reviewers using individual animal data^cMating index: No. of mated females expressed as % of no. of paired females^dFertility index: No. of pregnant females expressed % of no. of paired females^eFecundity index: No. of pregnant females expressed % of no. of mated females^fGestation index: No. of females delivering a live litter expressed as % of no. of pregnant females^gNumbers in parenthesis are the numbers of litters included in the calculation.^hLive birth index: Percentage of pups born alive based on no. of total pups bornⁱViability index: Percentage of pups surviving 4 days based on no. of pups born alive^jLactation index: Percentage of pups surviving 21 days based on no. of live pups on day 4 postcull

*Significant trend through indicated dosage (p<0.05)

TABLE 4. Effects of Exposure to MK-0244 on P₀ Reproductive Parameters and P_{1b} Offspring Survival and Body Weight^a

| Parameter | Observation at Each Exposure Level (mg/kg/day) | | | |
|--|--|-----------|-----------|-----------|
| | 0 | 0.1 | 0.6 | 3.6/1.8 |
| No. paired females | 33 | 33 | 32 | 33 |
| No. matings | 32 | 32 | 31 | 31 |
| Mating index (%) ^{b,c} | 97 | 97 | 97 | 94 |
| No. pregnant females | 28 | 28 | 26 | 23 |
| Fertility index (%) ^d | 85 | 85 | 81 | 70 |
| Fecundity index (%) ^e | 88 | 88 | 84 | 74 |
| Gestation index (%) ^f | 100 | 96 | 100 | 100 |
| Gestation length (days) | 22.2 | 22.4 | 22.4 | 22.4 |
| No. females with liveborn pups | 28 | 27 | 26 | 23 |
| Total no. live pups | | | | |
| Day 0 | 416 | 391 | 419 | 347 |
| Day 4, precull ^g | 393 | 377 | 407 | 336 |
| Day 21 ^h | 214 | 206 | 202 | 163 |
| Mean no. live pups/litter ⁱ | | | | |
| Day 0 | 14.9 (28) | 14.5 (27) | 16.1 (26) | 15.1 (23) |
| Day 4, precull ^g | 14.0 (28) | 14.0 (27) | 15.7 (26) | 14.6 (23) |
| Day 21 ^h | 7.6 (28) | 7.6 (27) | 7.8 (26) | 7.4 (22) |
| Live birth index (%) ^{b,h} | 95 | 99 | 99 | 98 |
| Viability index (%) ^{b,i} | 94 | 96 | 97 | 97 |
| Lactation index (%) ^{b,j} | 99 | 97 | 99 | 95 |
| Mean pup body weight (g), males | | | | |
| Day 0 | 6.5 | 6.7 | 6.7 | 6.8 |
| Day 7 | 16.6 | 16.9 | 17.4 | 17.8 |
| Day 21 | 57.9 | 59.4 | 61.5 | 60.2 |
| Mean pup body weight (g), females | | | | |
| Day 0 | 6.1 | 6.4 | 6.3 | 6.4 |
| Day 7 | 15.3 | 16.0 | 16.3 | 16.3 |
| Day 21 | 54.4 | 56.9 | 57.8 | 56.3 |
| Sex ratio (% males day 0) ^b | 50 | 51 | 51 | 49 |

^aData were extracted from Study No. TT 891-715-0, Tables A-34, A-35, and A-99.

^bCalculated (but not analyzed) by the reviewers using individual animal data

^cMating index: No. of mated females expressed as % of no. of paired females

^dFertility index: No. of pregnant females expressed % of no. of paired females

^eFecundity index: No. of pregnant females expressed % of no. of mated females

^fGestation index: No. of females delivering a live litter expressed as % of no. of pregnant females

^gNumbers in parenthesis are the numbers of litters included in the calculation.

^hLive birth index: Percentage of pups born alive based on no. of total pups born

ⁱViability index: Percentage of pups surviving 4 days based on no. of pups born alive

^jLactation index: Percentage of pups surviving 21 days based on no. of live pups on day 4 postcull

TABLE 5. Effects of Exposure to MK-0244 on F₁ Reproductive Parameters and F₂ Offspring Survival and Body Weight^a

| Parameter | Observation at Each Exposure Level (mg/kg/day) | | | |
|--|--|-----------|-----------|-----------|
| | 0 | 0.1 | 0.6 | 3.6/1.8 |
| No. paired females | 25 | 25 | 25 | 25 |
| No. matings | 25 | 23 | 22 | 23 |
| Mating index (%) ^{b,c} | 100 | 92 | 88 | 92 |
| No. pregnant females | 20 | 20 | 21 | 12 |
| Fertility index (%) ^d | 80 | 80 | 84 | 48* |
| Fecundity index (%) ^e | 80 | 87 | 95 | 52* |
| Gestation index (%) ^f | 95 | 100 | 95 | 92 |
| Gestation length (days) | 22.4 | 22.3 | 22.4 | 22.5 |
| No. females with liveborn pups | 19 | 20 | 20 | 11 |
| Total no. live pups | | | | |
| Day 0 | 265 | 271 | 307 | 162 |
| Day 4, precull ^g | 252 | 263 | 287 | 157 |
| Day 21 ^h | 129 | 137 | 131 | 83 |
| Mean no. live pups/litter ⁱ | | | | |
| Day 0 | 13.9 (19) | 13.6 (20) | 15.4 (20) | 14.7 (11) |
| Day 4, precull ^g | 13.3 (19) | 13.2 (20) | 14.4 (20) | 14.3 (11) |
| Day 21 ^h | 6.8 (19) | 7.2 (19) | 7.7 (20) | 7.5 (11) |
| Live birth index (%) ^{b,h} | 98 | 99 | 97 | 99 |
| Viability index (%) ^{b,j} | 95 | 97 | 93 | 97 |
| Lactation index (%) ^{b,j} | 88 | 94 | 86 | 94 |
| Mean pup body weight (g), males | | | | |
| Day 0 | 6.7 | 6.4 | 6.4 | 6.4 |
| Day 7 | 16.6 | 17.1 | 16.5 | 15.2 |
| Day 21 | 58.0 | 58.4 | 59.7 | 52.7* |
| Mean pup body weight (g), females | | | | |
| Day 0 | 6.3 | 6.2 | 6.1 | 6.1 |
| Day 7 | 15.4 | 16.6 | 15.4 | 14.8 |
| Day 21 | 54.8 | 57.5 | 57.4 | 51.0 |
| Sex ratio (% males day 0) ^b | 49 | 51 | 50 | 50 |

^aData were extracted from Study No. TT #91-715-0, Tables A-62, A-63, and A-126.^bCalculated (but not analyzed) by the reviewers using individual animal data^cMating index: No. of mated females expressed as % of no. of paired females^dFertility index: No. of pregnant females expressed % of no. of paired females^eFecundity index: No. of pregnant females expressed % of no. of mated females^fGestation index: No. of females delivering a live litter expressed as % of no. of pregnant females^gNumbers in parenthesis are the numbers of litters included in the calculation.^hLive birth index: Percentage of pups born alive based on no. of total pups bornⁱViability index: Percentage of pups surviving 4 days based on no. of pups born alive^jLactation index: Percentage of pups surviving 21 days based on no. of live pups on day 4 postcull*Significant trend through indicated dosage ($p < 0.05$)

TABLE 6. Physical Signs During Prewaning Period Exhibited By F_{1a}, F_{1b}, and F₂ Litters Exposed to MK-0244^a

| Parameter | Observation at Each Exposure Level (mg/kg/day) | | | |
|-------------------------------|--|-----|-----|---------|
| | 0 | 0.1 | 0.6 | 3.6/1.8 |
| <u>F_{1a} litters</u> | | | | |
| Number of litters examined | 30 | 22 | 25 | 22 |
| Hind limb extension | 0 | 0 | 0 | 21 |
| Hind limb splay | 0 | 0 | 0 | 18 |
| Intermittent head tremors | 0 | 0 | 0 | 20 |
| Limited use of hind limb(s) | 0 | 0 | 0 | 21 |
| Whole body tremors | 0 | 0 | 0 | 21 |
| <u>F_{1b} litters</u> | | | | |
| Number of litters examined | 28 | 27 | 26 | 23 |
| Hind limb extension | 0 | 0 | 0 | 5 |
| Hind limb splay | 0 | 1 | 0 | 0 |
| Intermittent head tremors | 0 | 0 | 0 | 0 |
| Limited use of hind limb(s) | 0 | 0 | 0 | 5 |
| Whole body tremors | 0 | 0 | 0 | 7 |
| <u>F₂ litters</u> | | | | |
| Number of litters examined | 19 | 19 | 19 | 11 |
| Hind limb extension | 0 | 0 | 0 | 1 |
| Hind limb splay | 0 | 0 | 0 | 0 |
| Intermittent head tremors | 0 | 0 | 0 | 0 |
| Limited use of hind limb(s) | 0 | 0 | 0 | 0 |
| Whole body tremors | 0 | 0 | 0 | 1 |

^aData were extracted from Study No. TT #91-715-0, Tables A-36, A-37, and A-64.



carolyn.brinkley@syngenta.com

09/21/2004 03:03 PM

To: Thomas Harris/DC/USEPA/US@EPA
cc: kimberly.clark@syngenta.com
Subject: FW: Emamectin standards

Tom, one of the conditions of a previous emamectin registration was for Syngenta to submit certain analytical standards to the EPA. I believe this completes what we owed the Agency.

Carolyn F. Brinkley
Sr. Regulatory Product Manager / Insecticides
Syngenta Crop Protection, Inc.
P.O. Box 18300
Greensboro, NC 27419-8300
Phone: (336) 632-2838
Fax: (336) 292-6374
Email: carolyn.brinkley@syngenta.com

> -----Original Message-----
> From: Hunt David A USGR
> Sent: Thursday, September 02, 2004 8:56 AM
> To: Brinkley Carolyn USGR
> Subject: Emamectin standards
>
> Carolyn,
>
> These standards have been shipped to Terry Cole at the EPA:
>
> <<04-101.doc>>
> David A. Hunt
>



04-101.doc

*Advance info
will be sent officially
via paper letter*



June 8, 2004

Document Processing Desk
Office of Pesticide Programs (H7505C)
U.S. Environmental Protection Agency
Room 266A, Crystal Mall 2
1921 Jefferson Davis Highway
Arlington, VA 22202-4501

ATTN: Thomas Harris Insecticide Rodenticide Branch

| | |
|--|-----------------------------|
| SUBJECT: Enamectin Benzoate Technical Submission of Final Printed Labeling In Response to EPA Acceptance Letter Dated February 23, 2004 | EPA REG. NO. 100-902 |
|--|-----------------------------|

Dear Mr. Harris:

Syngenta Crop Protection, Inc. hereby submits 3 copies of final printed labeling in response to the EPA acceptance letter dated February 23, 2004. This labeling incorporates the following changes to the Directions for Use site list that were required in the Agency letter:

- The term "turnip greens" has been expanded to "turnip greens (tops, leaves)".
- "Turnip greens (tops, leaves) only: For use on turnip varieties grown for leaves only. Do not use on turnip varieties grown for roots or dual-purpose varieties grown for roots and leaves." has been added as a footnote to the above phrase.

The miniature version shows layout of text as it appears on the actual container. The larger print copies are supplied to help facilitate review and duplication.

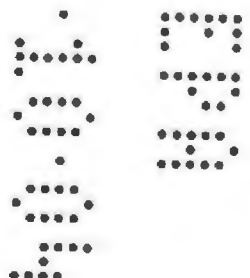
The label copy code is SCP 902A-L1G 0504.

If you have any questions please contact me at (336) 632- 2838.

Sincerely,

Carolyn Brinkley
Sr. Regulatory Product Manager
Regulatory Affairs

Enclosures: 1 copy of labeling (miniature)
2 copies of labeling (large print)
EPA form 8570-1





United States
Environmental Protection Agency
Washington, DC 20460

☐ Registration
☐ Amendment
☒ Other

OPP Identifier Number

Application for Pesticide - Section I

| | | |
|---|---|--|
| 1. Company/Product Number 100-902 | 2. EPA Product Manager Thomas Harris | 3. Proposed Classification <input checked="" type="checkbox"/> None <input type="checkbox"/> Restricted |
| 4. Company/Product (Name) Emamectin Benzoate Technical | PM# IRB | |
| 5. Name and Address of Applicant (Include ZIP Code) Syngenta Crop Protection, Inc. P. O. Box 18300 Greensboro, NC 27419 <input type="checkbox"/> Check if this is a new address | 6. Expedited Review. In accordance with FIFRA Section 3(c)(3) (b)(i), my product is similar or identical in composition and labeling to: EPA Reg. No. _____ Product Name _____ | |

Section - II

| | |
|--|---|
| <input type="checkbox"/> Amendment - Explain below. | <input checked="" type="checkbox"/> Final printed labels in response to Agency letter dated February 23, 2004 |
| <input type="checkbox"/> Resubmission in response to Agency letter dated _____ | <input type="checkbox"/> "Me Too" Application. |
| <input type="checkbox"/> Notification - Explain below. | <input type="checkbox"/> Other - Explain below. |

Explanation: Use additional page(s) if necessary. (For Section I and Section II.)

Syngenta Crop Protection, Inc. hereby submits 3 copies of final printed labeling in response to the EPA acceptance letter dated February 23, 2004. This labeling incorporates the following changes to the Directions for Use site list that were required in the Agency letter:

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The miniature version shows layout of text as it appears on the actual container. The larger print copies are supplied to help facilitate review and duplication. The label copy code is SCP 902A-L1G 0504.

Section - III

| | | | | | |
|---|---|---|--|-----------------------------|--|
| 1. Material This Product Will Be Packaged In: | | | | 2. Type of Container | |
| Child-Resistant Packaging <input type="checkbox"/> Yes* <input type="checkbox"/> No | Unit Packaging <input type="checkbox"/> Yes <input type="checkbox"/> No | Water Soluble Packaging <input type="checkbox"/> Yes <input type="checkbox"/> No | <input type="checkbox"/> Metal <input type="checkbox"/> Plastic <input type="checkbox"/> Glass <input type="checkbox"/> Paper <input type="checkbox"/> Other (Specify) _____ | | |
| *Certification must be submitted | If "Yes" Unit Packaging wgt. No. per Container | If "Yes" Unit Packaging wgt. No. per container | | | |
| 3. Location of Net Contents Information <input type="checkbox"/> Label <input type="checkbox"/> Container | 4. Size(s) Retail Container | 5. Location of Label Directions <input type="checkbox"/> On Label <input type="checkbox"/> On Labeling accompanying product | | | |
| 6. Manner in Which Label is Affixed to Product <input type="checkbox"/> Lithograph <input type="checkbox"/> Paper glued <input type="checkbox"/> Stenciled <input type="checkbox"/> Other _____ | | | | | |

Section - IV

| | | | | | |
|--|--|--|--|---|--|
| 1. Contact Point (Complete items directly below for identification of individual to be contacted, if necessary, to process this application.) | | | | | |
| Name Carolyn F. Brinkley | | Title Sr. Regulatory Product Manager Insecticides | | Telephone No. (Include Area Code) (336) 632-2838 | |
| Certification I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law. | | | | | 6. Date Application Received (Stamp) |
| 2. Signature | | 3. Title Sr. Regulatory Product Manager Insecticides | | | |
| 4. Typed Name Carolyn F. Brinkley | | 5. Date June 8, 2004 | | | |

EPA Form 8570-1 (Rev. 8-94) Previous editions are obsolete.

NOT REVIEWED
In accordance with PR Notice 82-2
Based on Draft Labeling Dated

FEB 23 2004

Emamectin Benzoate Technical

An insecticide for formulation into end-use
insecticide products intended for non-domestic
terrestrial outdoor food use.

| | |
|--|--------|
| Active Ingredient: | |
| Emamectin Benzoate (CAS No. 155569-91-8) | 97.0% |
| Other Ingredients: | 3.0% |
| Total: | 100.0% |

KEEP OUT OF REACH OF CHILDREN. DANGER/PELIGRO

Si usted no entiende la etiqueta, busque a alguien para que se la explique a
usted en detalle. (If you do not understand the label, find someone to
explain it to you in detail.)

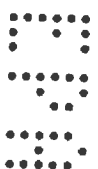
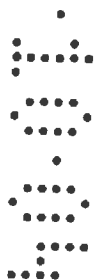
See additional precautionary statements on label.

EPA Reg. No. 100-902
EPA Est. 41448-SW-1

Product of Switzerland

Product ID. **28075**

Net Contents



FIRST AID

If in eyes: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.

If swallowed: Call a poison control center or doctor immediately for treatment advice. Have person sip glass of water if able to swallow. Do not induce vomiting unless told to do so by a poison control center or doctor. Do not give anything by mouth to an unconscious person.

If on skin or clothing: Take off contaminated clothing. Rinse skin immediately with plenty of water for 15-20 minutes. Call a poison control center or doctor for treatment advice.

If inhaled: Move person to fresh air. If person is not breathing, call 911 or an ambulance, and then give artificial respiration, preferably mouth-to-mouth, if possible. Call a poison control center or doctor for treatment advice.

NOTE TO PHYSICIAN: Probable mucosal damage may contraindicate the use of gastric lavage. Early signs of intoxication include dilated pupils, muscular incoordination, and muscle tremors. If toxicity from exposure has progressed to cause severe vomiting, the extent of resultant fluid and electrolyte imbalance should be gauged. Appropriate supportive parenteral fluid replacement therapy should be given, along with other required supportive measures (such as maintenance of blood pressure levels and proper respiratory function) as indicated by clinical signs, symptoms, and measurements.

In severe cases, observations should continue for at least several days until clinical condition is stable and normal. Since enamectin benzoate is believed to enhance GABA activity in animals, it is probably wise to avoid drugs that enhance GABA activity (barbiturates, benzodiazepines, valproic acid) in patients with potentially toxic enamectin benzoate exposure.

Have the product container or label with you when calling a poison control center or doctor, or going for treatment.

HOT LINE NUMBER: For 24 Hour Medical Emergency Assistance (Human or Animal) or Chemical Emergency Assistance (Spill, Leak, Fire, or Accident), Call 1-800-888-8372.

PRECAUTIONARY STATEMENTS

Hazards to Humans and Domestic Animals

ANGER/PELIGRO

Corrosive. Causes irreversible eye damage. Do not get in eyes or on clothing. Wear protective eyewear (goggles, face shield, or safety glasses). May be fatal if swallowed. Wash thoroughly with soap and water after handling and before eating, drinking, or using tobacco. Remove and wash contaminated clothing before reuse.

Environmental Hazards

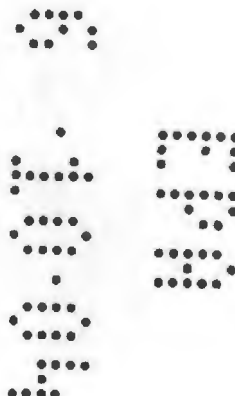
This pesticide is toxic to fish, birds, mammals, and aquatic invertebrates. Do not discharge effluent containing this active ingredient into lakes, streams, ponds, estuaries, oceans, or other public waters, unless in accordance with the requirements of a National Pollutant Discharge Elimination System (NPDES) permit, and the permitting authority has been notified in writing prior to discharge. Do not discharge effluent containing this product into sewer systems without previously notifying the local sewage treatment plant authority. For guidance, contact your State Water Board or Regional Office of the EPA.

CONDITIONS OF SALE AND LIMITATION OF WARRANTY AND LIABILITY

NOTICE: Read the entire Directions for Use and Conditions of Sale and Limitation of Warranty and Liability before buying or using this product. If the terms are not acceptable, return the product at once, unopened, and the purchase price will be refunded.

The Directions for Use of this product should be followed carefully. It is impossible to eliminate all risks inherently associated with the use of this product. Crop injury, ineffectiveness or other unintended consequences may result because of such factors as manner of use or application, weather or crop conditions, presence of other materials or other influencing factors in the use of the product, which are beyond the control of SYNGENTA CROP PROTECTION, Inc. or Seller. All such risks shall be assumed by Buyer and User, and Buyer and User agree to hold SYNGENTA and Seller harmless for any claims relating to such factors.

SYNGENTA warrants that this product conforms to the chemical description on the label and is reasonably fit for the purposes stated in the Directions for Use, subject to the inherent risks referred to above, when used in accordance with directions under normal use conditions. This warranty does not extend to the use of the product contrary to label instructions, or under abnormal conditions or under conditions not reasonably foreseeable to or beyond the control of Seller or SYNGENTA, and Buyer and User assume the risk of any



such use. SYNGENTA MAKES NO WARRANTIES OF MERCHANTABILITY OR OF FITNESS FOR A PARTICULAR PURPOSE NOR ANY OTHER EXPRESS OR IMPLIED WARRANTY EXCEPT AS STATED ABOVE.

In no event shall SYNGENTA or Seller be liable for any incidental, consequential or special damages resulting from the use or handling of this product. THE EXCLUSIVE REMEDY OF THE USER OR BUYER, AND THE EXCLUSIVE LIABILITY OF SYNGENTA AND SELLER FOR ANY AND ALL CLAIMS, LOSSES, INJURIES OR DAMAGES (INCLUDING CLAIMS BASED ON BREACH OF WARRANTY, CONTRACT, NEGLIGENCE, TORT, STRICT LIABILITY OR OTHERWISE) RESULTING FROM THE USE OR HANDLING OF THIS PRODUCT, SHALL BE THE RETURN OF THE PURCHASE PRICE OF THE PRODUCT OR, AT THE ELECTION OF SYNGENTA OR SELLER, THE REPLACEMENT OF THE PRODUCT.

SYNGENTA and Seller offer this product, and Buyer and User accept it, subject to the foregoing Conditions of Sale and Limitation of Warranty and of Liability, which may not be modified except by written agreement signed by a duly authorized representative of SYNGENTA.

DIRECTIONS FOR USE

It is a violation of Federal law to use this product in a manner inconsistent with its labeling.

This product may be used only for the formulation of end-use insecticide products registered by the EPA for use on leafy vegetables, including *Brassica*, turnip greens (tops, leaves)*, fruiting vegetables, cotton, and tobacco.

*Turnip Greens (tops, leaves) only: for use on turnip varieties grown for leaves only. Do not use on turnip varieties grown for roots or dual-purpose varieties grown for roots and leaves.

STORAGE AND DISPOSAL

Do not contaminate water, food, or feed by storage or disposal.

Pesticide Storage

Store in a tightly closed original container in a cool, dry place. Do not store near food or feed.

Pesticide Disposal

Pesticide wastes are acutely hazardous. Improper disposal of excess pesticide, or rinse is a violation of Federal law. If these wastes cannot be disposed of by use according to label instructions, contact your State Pesticide or Environmental Control Agency, or the Hazardous Waste representative at the nearest EPA Regional Office for guidance. Pesticide that cannot be used or chemically reprocessed must be disposed of according to federal, state, or local procedures under the Resource Conservation and Recovery Act.

Container Disposal

Bulk: Thoroughly clean container before reuse. Consult federal, state, or local disposal authorities for approved alternative procedures.

250 Gal. Mini Bulk: This is a refillable container that must be returned to an authorized Syngenta refilling facility for refilling or disposal. Before refilling, inspect thoroughly for damage such as cracks, punctures, bulges, dents, abrasions, and damaged or worn threads on closure devices. After filling and before transporting, check for leaks. Do not refill or transport damaged or leaking container.

Other Containers: Triple rinse (or equivalent). Then offer for recycling or reconditioning, or puncture and dispose of in a sanitary landfill, or by other procedures approved by state and local authorities.

CONTAINER IS NOT SAFE FOR FOOD, FEED, OR DRINKING WATER.

Note: For minor spills, leaks, etc. follow all precautions indicated on this label and clean up immediately. Take special care to avoid contamination of equipment and facilities during clean up and disposal of wastes.

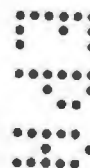
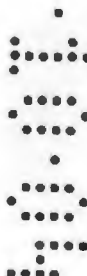
Emamectin Benzoate Technical and the Syngenta logo are trademarks of a Syngenta Group Company.

©2004 Syngenta

For non-emergency (e.g. current product information)
call Syngenta Crop Protection, Inc. at 1-800-334-9481

Syngenta Crop Protection, Inc.
Greensboro, North Carolina 27409
www.syngenta-us.com

SCP 902A-L1G 0504
L112040 USA/SH





Thomas Harris

06/09/2004 03:22 PM

To: Meredith Laws/DC/USEPA/US@EPA, Paula

Deschamp/DC/USEPA/US@EPA, John Hebert/DC/USEPA/US@EPA

cc:

Subject: Letters of Authorization for Schering-Plough

I'm assuming from the note below that HED has already been asked about this and HED wanted the letters of authorization. Here they are. Let me know if EPA needs anything else from Syngenta on this.

I'll print and file this in the emamectin technical (100-902) jacket.

Tom Harris

EPA/OPPTS/OPP/RD/IRB

(703) 308-9423

harris.thomas@epa.gov

visit <http://www.epa.gov/pesticides>

--- Forwarded by Thomas Harris/DC/USEPA/US on 06/09/2004 03:23 PM ---



carolyn.brinkley@syngenta.com

06/09/2004 02:28 PM

To: Thomas Harris/DC/USEPA/US@EPA

cc: katrina.brodie@syngenta.com, richard.endris@spcorp.com

Subject: Letters of Authorization for Schering-Plough

Dear Tom:

Schering-Plough Animal Health has an action at the FDA pending approval. This action is for the approval of an emamectin-based product that is fed to farm-raised fish for the control of sea lice. The FDA wants to discuss the 2-generation reproduction study for emamectin with the EPA. However, the EPA indicated to Schering-Plough that Syngenta's permission would be needed before the Agency discussed the study with the FDA. The attached letters explain the authorization and allow EPA and FDA to discuss this study. Would you please forward this to HED on Schering-Plough's behalf? If you have any questions, please call. Thanks for your assistance.

<<EPAAuthLetterReScheringEmamectinJune7'04.doc>>

<<EPACoverLetterReScheringEmamectinJune04.doc>>



EPAAuthLetterReScheringEmamectinJune7'0- EPACoverLetterReScheringEmamectinJune0-



Carolyn F. Brinkley
Sr. Regulatory Product Manager
Regulatory Affairs
carolyn.brinkley@syngenta.com
(336) 632 2838

Syngenta Crop Protection, Inc.
P. O. Box 18300
410 Swing Road
Greensboro, NC 27419-8300

June 7, 2004

Mr. Thomas Harris
Insecticide-Rodenticide Branch
U.S. Environmental Protection Agency
Office of Pesticide Programs
Ariel Rios Building
1200 Pennsylvania Ave, NW
Washington, DC 20460-0001

**SUBJECT: EMAMECTIN BENZOATE TECHNICAL
EPA REG. NO. 100-902
AUTHORIZATION FOR EPA-FDA DISCUSSION OF SPECIFIED
TWO-GENERATION REPRODUCTION STUDY**

Dear Mr. Harris:

Syngenta Crop Protection, Inc. hereby authorizes toxicologists with the Office of Pesticide Programs Health Effects Division of the U.S. Environmental Protection Agency to discuss the below-cited study with FDA toxicologists. This authorization is limited to a discussion of this study, solely with respect to Schering-Plough Animal Health's application for FDA approval of an emamectin-based product known as Slice™ (emamectin benzoate 0.2% Type A medicated article for salmon), INAD 010-418). Slice™ is proposed for use in the feed of farm-raised fish primarily for the control of sea lice.

EPA MRID No.
42851511

CITATION
Lankas, G. (1993) MK-0244: Two-Generation Dietary Reproduction Study in Rats: Lab Project Number: 618-244-TOX49: TT #91-715-0: AS-3446. Unpublished study prepared by Merck Research Labs.

This authorization is qualified to the extent, however, that: (1) neither Schering-Plough Animal Health, nor any person other than the Administrator shall have access to or reference said data, and/or EPA MRID number unless specific authorization to that effect is provided in writing by Syngenta Crop Protection, Inc. (2) this authorization shall not be construed as authorization for the EPA to discuss with the FDA any Syngenta data, directly or indirectly, in support of any subsequent application submitted by Schering-Plough Animal Health or any other person to the FDA or the EPA including, without limitation, applications for

new registration or amended registration (3) this authorization shall not be transferred by Schering-Plough Animal Health in any manner whatsoever without express prior written consent of Syngenta and (4) this authorization shall terminate upon the conclusion of discussion of the study between EPA and FDA.

Sincerely,



Carolyn F. Brinkley
Sr. Regulatory Product Manager
Regulatory Affairs

cc: Dr. Louis T. Mulligan
Team Leader - Toxicology Team
Division of Human Food Safety (HFV-150)
C/O Document Control Unit (HFV-199)
Center for Veterinary Medicine
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

bcc: K Brodie/customer service file/Schering-Plough
S. Reasons
C. Moseley
C. Biggers



Carolyn F. Brinkley
Sr. Regulatory Product Manager
Regulatory Affairs
carolyn.brinkley@syngenta.com
(336) 632 2838

Syngenta Crop Protection, Inc.
P. O. Box 18300
410 Swing Road
Greensboro, NC 27419-8300

June 7, 2004

Mr. Thomas Harris
Insecticides-Rodenticides Branch
Office of Pesticide Programs (7504C)
U.S. Environmental Protection Agency
Ariel Rios Building
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460

**SUBJECT: EMAMECTIN BENZOATE TECHNICAL
EPA REG. NO. 100-902
ATTACHED AUTHORIZATION FOR EPA-FDA DISCUSSION OF
SPECIFIED 2-GENERATION REPRODUCTION STUDY**

Dear Mr. Harris:

Schering-Plough Animal Health, is pursuing an FDA approval of an emamectin – based product known as Slice™ (emamectin benzoate 0.2% Type A medicated article for salmon), INAD 010-418). Slice™ is proposed for use in the feed of farm-raised fish primarily for the control of sea lice. One of the studies that is needed to support this FDA approval of emamectin is on file with the EPA and supports Syngenta Crop Protection, Inc.'s. registrations of emamectin benzoate on crops. The study is:

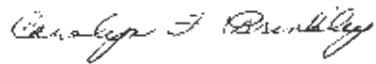
EPA MRID No.
42851511

CITATION
Lankas, G. (1993) MK-0244: Two-Generation Dietary Reproduction Study in Rats: Lab Project Number: 618-244-TOX49; TT #91-715-0; AS-3446.
Unpublished study prepared by Merck Research Labs.

The FDA scientist reviewing the supporting data for the approval of Slice™ would like to discuss this study with a member of the EPA's Health Effects Division. It is Syngenta's understanding that the EPA requires Syngenta's authorization prior to this discussion. The enclosed letter authorizes the FDA and EPA scientists to discuss this specific study with emamectin with respect to Schering-Plough's pending application for FDA approval of Slice™. This authorization is limited solely to a discussion of the specified study and is further limited only to the pending approval for Slice™. The attached letter of authorization further clarifies these

conditions. If you have any questions or comments about this label, please contact me. I can be reached at (336) 632-2838.

Sincerely yours,



Carolyn F. Brinkley
Sr. Regulatory Product Manager
Regulatory Affairs

cc: Dr. Louis T. Mulligan
Team Leader - Toxicology Team
Division of Human Food Safety (HFV-150)
C/O Document Control Unit (HFV-199)
Center for Veterinary Medicine
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

bcc: C. Biggers
K. Brodie/customer service file Schering-Plough
S. Reasons
C. Moseley



55 H 4. 2

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Harvard

April 30, 2004

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

PLEASE RETURN A COPY OF THIS LETTER WITH PAYMENT

OPP Decision Number: D-174279
EPA File Symbol or Registration Number: 100-902
Product Name: EMAMECTIN BENZOATE TECHNICAL
EPA Receipt Date: 02-Apr-2003
EPA Company Number: 100
Company Name: SYNGENTA CROP PROTECTION, INC.

G. THOMAS GALE, JR.
SYNGENTA CROP PROTECTION, INC.
ATTN: REGULATORY AFFAIRS
PO Box 18300
GREENSBORO, NC 27419-8300

SUBJECT: Receipt of Registration Service Fee Voluntary Payment Notice

Dear Registrant:

The Office of Pesticide Programs has received your Notice of Intent to Submit Voluntary Payment for the action described below.

The Action has been identified as Action Code: R17.2

NEW USE; EACH ADDITIONAL NEW FOOD USE; TWO NEW USES;

The net amount due was calculated by determining the fee associated with this action (from the March 17, 2004 Federal Register Notice), calculating the amount of work that has been completed on the particular action, and reducing the basic fee by the appropriate percentage of work completed. This amount was further reduced by the amount of any tolerance fee paid in association with this action if applicable.

You may be eligible for a full or partial waiver of the fee. Refer to OPP's Fee for Service web site at www.epa.gov/pesticides/fees for guidance on how to request a waiver.

Please remit payment in the amount of: \$ 72,968 to:

By USPS:

USEPA Washington Finance Center
Pesticide Registration Service Fee
PO Box 360277
Pittsburgh, PA 15251

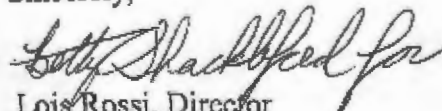
By Courier:

U.S. EPA Washington Finance Center
Pesticide Registration Service Fee
C/O Mellon Client Service Center
500 Ross Street, Room 670
Box 360277
Pittsburgh, PA 15251-6277
Attn: EPA Module Supervisor

All payments must be in United States currency by check, bank draft, or money order drawn to the order of the Environmental Protection Agency. To ensure proper credit, please write the OPP DECISION NUMBER on your check, and enclose a copy of this letter with your payment.

If you have any questions, please contact the Pesticide Registration Service Fee Ombudsman at (703) 305-6249.

Sincerely,


Lois Rossi, Director
Registration Division

Voluntary

FEE FOR SERVICE

DIVISION: RD

PRODUCT /RISK MANAGER: 07

EPA FILE SYMBOL/REG. NO.: 120-902

PIN-PUNCH DATE: 3/26/04

ACTION CODE: R17

AMOUNT DUE:

100,000
18,925 Tol. Fee pd.

81,075.00
-8,107.50

72,967.50

Pome fruit counts as 2 new uses
50k x 2 = 100k
10% of work complete

WAIVER REQUEST

D 174279

- ☐ Small Business 100%
- ☐ Small Business 50%
- ☐ IR4
- ☐ Minor Use
- ☐ Federal/State

REVIEWER: M Lewis

REMARKS:

No work has been done on this

S: 757027

Regulatory Type: Product Registration - Section 3

Resubmission: ☒ Yes ☐ No

Application Type: Voluntary Fee Payment

Fee For Service: ☒ Yes ☐ No

Company: 100 SYNGENTA CROP PROTECTION, INC.

V

Risk Manager: Registration Division, Risk Management Team 7

Product #: 100-902

Product Name: EMAMECTIN BENZOATE TECHNICAL

Owner del:

Me Too
Section 3:

Me Too
Product Name:

Application Date: 23-Mar-2004

icj

OPP Rec'd Date: 26-Mar-2004

icj

Front End Date: 26-Mar-2004

icj

Risk Manager Send Date: 29-Mar-2004

icj

Fast Track: ☐

New Ingredient: ☐

Receipt Description:

New Ingredient

Received Date

New Ingredient

Received Date

Form A:

☐

Signature Date:

Form B:

☐

Signature Date:

Receipt Content



United States
Environmental Protection Agency
Washington, DC 20460

☐ Registration
☐ Amendment
☒ Other

OPP Identifier Number

Application for Pesticide - Section I

| | | |
|---|---|--|
| 1. Company/Product Number 100-902 | 2. EPA Product Manager John Hebert | 3. Proposed Classification <input checked="" type="checkbox"/> None <input type="checkbox"/> Restricted |
| 4. Company/Product (Name) Emamectin Benzoate (Proclaim Insecticide EPA Reg #100-904; Denim Insecticide EPA Reg #100-903) | PM# 4 | |
| 5. Name and Address of Applicant (Include ZIP Code) Syngenta Crop Protection, Inc. P. O. Box 18300 Greensboro, NC 27419 <input type="checkbox"/> Check if this is a new address | 6. Expedited Review. In accordance with FIFRA Section 3(c)(3) (b)(i), my product is similar or identical in composition and labeling to: EPA Reg. No. _____ Product Name _____ | |

Section - II

- ☐ Amendment - Explain below. ☐ Final printed labels in response to Agency letter dated _____
- ☐ Resubmission in response to Agency letter dated _____ ☐ "Me Too" Application.
- ☐ Notification - Explain below. ☒ Other - Explain below.

Explanation: Use additional page(s) if necessary. (For Section I and Section II.)

VOLPAY

Offering Voluntary Fee Payment under PRIA for Emamectin Benzoate (EPA Reg. # 100-902) requesting tolerances for emamectin on members of the Pome Fruit Group. Submitted 3/31/2003. PP No. 3F6574

R17/72 \$50,000; a check for \$18,925 was submitted earlier to EPA for tolerance fees associated with this petition.

E-mail: Carolyn.Brinkley@syngenta.com

Fax: 1-336-292-6374

Section - III

| | | | | | |
|---|---|--|--|---|--|
| 1. Material This Product Will Be Packaged In: | | | | 2. Type of Container | |
| Child-Resistant Packaging <input type="checkbox"/> Yes* <input type="checkbox"/> No | Unit Packaging <input type="checkbox"/> Yes <input type="checkbox"/> No | Water Soluble Packaging <input type="checkbox"/> Yes <input type="checkbox"/> No | <input type="checkbox"/> Metal <input type="checkbox"/> Plastic <input type="checkbox"/> Glass <input type="checkbox"/> Paper <input type="checkbox"/> Other (Specify) _____ | | |
| Certification must be submitted If "Yes" Unit Packaging wgt. No. per container | | If "Yes" Unit Packaging wgt. No. per container | | | |
| 3. Location of Net Contents Information <input type="checkbox"/> Label <input type="checkbox"/> Container | | 4. Size(s) Retail Container | | 5. Location of Label Directions <input type="checkbox"/> On Label <input type="checkbox"/> On Labeling accompanying product | |
| 6. Manner in Which Label is Affixed to Product <input type="checkbox"/> Lithograph <input type="checkbox"/> Paper glued <input type="checkbox"/> Stenciled | | <input type="checkbox"/> Other _____ | | | |

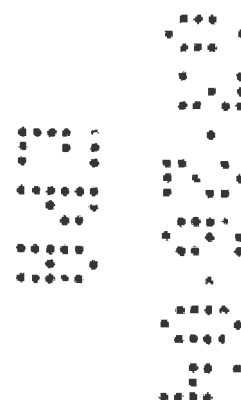
Section - IV

| | | | | | |
|--|--|---|--|--|--|
| 1. Contact Point (Complete items directly below for identification of individual to be contacted, if necessary, to process this application.) | | | | | |
| Name Carolyn F. Brinkley | | Title Senior Regulatory Product Manager | | Phone: 1-336-632-2838 | |
| Certification I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law. | | | | 6. Date Application Received (Stamped) | |
| 2. Signature | | 3. Title Senior Regulatory Product Manager | | | |
| 4. Typed Name Carolyn F. Brinkley | | 5. Date 3/23/2004 | | | |



March 28, 2003

Document Processing Desk (PETN)
Office of Pesticide Programs (7504C)
U.S. Environmental Protection Agency
401 M Street S.W.
Washington, DC 20460



Attention: Mr. Thomas Harris, Insecticides Rodenticides Branch

**SUBJECT: PETITION FOR TOLERANCES OF EMAMECTIN BENZOATE
IN OR ON POME FRUIT - 40 CFR 180.505**

Dear Mr. Harris,

Syngenta Crop Protection, Inc. is submitting a petition for the establishment of tolerances of emamectin benzoate in or on pome fruit (Crop Group 11) in 40 CFR 180.505.

In a separate submission we are submitting an application to amend the Proclaim Insecticide label (EPA Reg. No. 100-904) to add directions for use on pome fruit. In Syngenta's recent letter to the EPA regarding the Agency's FY 2004 work plan Syngenta listed this petition as one of its priorities. Syngenta also plans to submit, by June 1, 2003, a rationale supporting the classification of this proposed use as an organophosphate replacement.

The accompanying residue studies in apples and pears, the representative commodities for the pome fruit crop group, support the petition for tolerances:

| Commodity | Proposed Tolerance (ppm) |
|----------------------------|---|
| Pome Fruit (Crop Group 11) | 0.02 ppm |
| Apple pomace (wet) | Residue data indicate that no tolerance is needed |
| Apple/Pear Juice | |

In addition to the enclosed petition for tolerance Syngenta is submitting the following:

1. Crop residue data in apples and pears
2. A Notice of Filing as required by the FQPA for publication in the Federal Register.

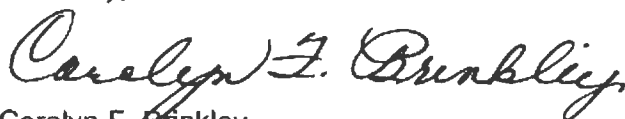
Based on the March 13, 2002 Federal Register Notice "Pesticide Tolerance Processing Fees", we calculated the required fees for this tolerance as follows:

| Highest Existing Tolerance | Proposed Tolerance | Required Fee | Justification for Fee Section 180.33 (b& h) 2002 FR Notice |
|----------------------------|---|---|--|
| 0.025 ppm | 0.02 ppm - pome fruit crop group No tolerance required for apple pomace or juice based on residue study results. | \$17,750 + <u>\$ 1,175</u> \$18,925 | Each petition or request for establishment of a tolerance at a lower numerical level or levels than a tolerance already established for the same pesticide chemical shall be accompanied by a fee of \$17,750 plus \$1,175 for each raw agricultural commodity on which a tolerance is requested. Each petition or request for a crop group tolerance, regardless of the number of raw agricultural commodities, shall be accompanied by a fee equal to the fee required by the analogous category for a single tolerance that is not a group tolerance. |

Syngenta is sending a copy of this letter and a check in the amount of \$18,925 to the EPA Headquarters Accounting Operations Branch in Pittsburgh, PA.

Thank you for your consideration of this petition. If you have any questions, please contact me at (336) 632-2391 or via e-mail at carolyn.brinkley@syngenta.com.

Sincerely,



Carolyn F. Brinkley
Sr. Regulatory Product Manager
Regulatory Affairs

cc: EPA Headquarters Accounting Operations Branch

Enclosures: Volume 1 of 2 - Transmittal Document

Volume 2 of 2 - Enamectin Benzoate Final Report - MK-0224 -
Magnitude of the Residues in on on Crop Group 11: Pome Fruit

Petition for Tolerance

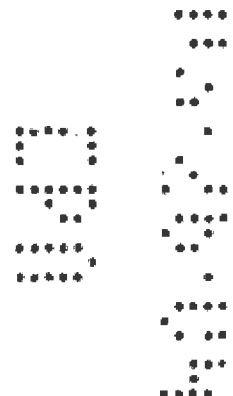
Syngenta Crop Protection, Inc Tel 336 632 6000
P.O. Box 18300
Greensboro, NC 27419-8300

Carolyn F. Brinkley
Sr. Regulatory Product Manager
Syngenta Crop Protection, Inc
Phone: (336) 632-2838
Fax: (336) 292-6374
E-mail: carolyn.brinkley@syngenta.com

Confidential

July 21, 2003

Document Processing Desk [AMEND]
Office of Pesticide Programs (7504C)
U.S. Environmental Protection Agency
Ariel Rios Building
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460



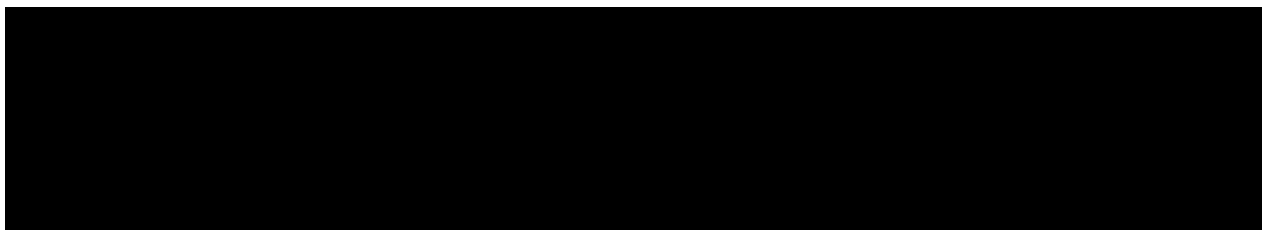
Attention: Mr. Thomas Harris
Insecticide-Rodenticide Branch

**SUBJECT: EMAMECTIN BENZOATE TECHNICAL
EPA REG. NO. 100-902
NEW SPECIFICATIONS BASED ON FULL-SCALE PRODUCTION IN
SWITZERLAND**

Gentlemen:

In 2001 Syngenta Crop Protection, Inc. submitted a revised basic and alternate confidential statement of formula and supporting product chemistry data for Emamectin Benzoate Technical, EPA Reg. No. 100-902. The purpose of the revision was to change the production location from the United States to Switzerland. The data that were submitted in 2001 were based on pilot scale production data. Now that full-scale production for Emamectin Technical has been ongoing in Switzerland for approximately one year the preliminary analysis, by-products and certified limits for emamectin benzoate have been refined. Therefore, Syngenta is submitting an addendum to the product chemistry data submitted to the EPA in 2001 (EPA MRID No. 45420801) and a revised basic and alternate confidential statement of formula for Emamectin Benzoate Technical.

Because the specifications of Emamectin Benzoate Technical are confidential, please consider the information in this letter and the accompanying data CBI. The changes are summarized as follows:



[REDACTED]

The attached Data Sheet explains these changes in greater detail. If you have any questions about these revisions, please contact me. I can be reached at (336) 632 2838.

Sincerely,

Carolyn F. Brinkley
Sr. Regulatory Product Manager
Regulatory Affairs

Enclosures: Volume 1 of 2 – Transmittal Document
Volume 2 of 2 – Manufacturing Process Description and Supporting Data for
Emamectin Benzoate Technical (Addendum to MRID
45420801)

bcc: Kimberly Clark
RA file 100-902/Updated CSF 7-21-03

Syngenta Crop Protection, Inc Tel 336 632 6000
P.O. Box 18300
Greensboro, NC 27419-8300

Carolyn F. Brinkley
Sr. Regulatory Product Manager
Syngenta Crop Protection, Inc
Phone: (336) 632-2838
Fax: (336) 292-6374
E-mail: carolyn.brinkley@syngenta.com

May 18, 2001

Document Processing Desk [AMEND]
Office of Pesticide Programs (7504C)
U.S. Environmental Protection Agency
Ariel Rios Building
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460

Attention: Mr. Thomas Harris
Insecticide-Rodenticide Branch

**SUBJECT: EMAMECTIN BENZOATE TECHNICAL, EPA REG. NO. 100-902
CHANGE IN MANUFACTURER OF ACTIVE INGREDIENT
REVISED CSF & SUPPORTING DATA**

Gentlemen:

Technical emamectin benzoate was previously registered by Merck. The registration has since been transferred to Syngenta Crop Protection and Syngenta will be producing the product in the future. For this reason, Syngenta generated new product chemistry data that include new analytical methods. The enclosed confidential statement of formula is based on these data.

Approval of the revised confidential statement of formula by August is needed to insure that we can meet our upcoming production requirements and your review of this submission will be appreciated. If you have any questions or comments, please contact me. I can be reached at (336) 632-2838.

Sincerely yours,

Carolyn F. Brinkley
Sr. Regulatory Product Manager
Regulatory Affairs

Enclosures: EPA Application for Pesticide Amendment
Volume 1 of 2 – Transmittal Document
Volume 2 of 2 – Manufacturing Process Description and Supporting Data for
Emamectin Benzoate Technical (Product Chemistry Group A
Data)

bcc: J. Reynolds/L. Phelps
S. Miller
C. Savinelli
RA file 100-902/Revised CSF + data



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

April 29, 2004

Carolyn Brinkley
Syngenta Crop Protection, Inc.
PO Box 18300
Greensboro, NC 27419

Subject: Enamectin Technical, EPA Reg. # 100-902
revised CSFs dated 11/5/05 (submitted 7/21/03)
accepted

Dear Ms. Brinkley,

The Agency has reviewed your submission for a revised Confidential Statement of Formula (CSF). The Confidential Statements of Formula dated 11/5/02 for both a basic and an alternate formulation are acceptable. Alternate ingredients were found to be similar to previous ingredients. The ingredient percentages and limits comply with PR Notice 91-2. Enclosed please find a copy of the review by BKitchens dated 4/27/04.

These basic and alternate Confidential Statements of Formula have been added to your file as part of the record. These replace all previous CSFs for this product.

If you have any questions please contact me at (703) 308-9423 or
Harris.Thomas@EPA.gov.

Sincerely yours,

151

Thomas C. Harris
Insecticide / Rodenticide Branch
Registration Division (7505C)
Office of Pesticide Programs

enclosure

DATE OUT: 27 Apr 2004

SUBJECT: EP [] MP [x] PRODUCT CHEMISTRY REVIEW
DP BARCODE No.: D299038
REG./File Symbol No.: 100-902
PRODUCT NAME: Emamectin Benzoate Technical
COMPANY: Syngenta Crop Protection, Inc.
FOOD USE: [] PC CODE: 122806
Decision No. 339531 Integrated Formulation [x]

TO: RM #07, Thomas Harris/John Hebert
Insecticide-Rodenticide Branch
Registration Division (7505C)

FROM: Bruce F. Kitchens, Chemist
Technical Review Branch
Registration Division (7505C)

Bruce F. Kitchens
27 Apr 2004
SPB 4/27/04

INTRODUCTION:

The registrant, Syngenta Crop Protection, Incorporated, is submitting revised basic and alternate Confidential Statements of Formula (CSFs) for the registered manufacturing use product, Emamectin Benzoate Technical. This revision is the result of additional data obtained from full scale production facilities in Switzerland. The active ingredient in this product is Emamectin Benzoate Technical at a label nominal concentration of 97.0% a.i. This product is intended for use in the manufacture of insecticide end-use products. With this submission, the registrant has submitted basic and alternate CSFs both dated 05 Nov 2002 and product chemistry data contained in MRID# 460449-01. This data is an addendum to product chemistry data contained in MRID# 454208-01. The Technical Review Branch (TRB) has been asked to review this submission.

SUMMARY OF FINDINGS:

TRB has reviewed this submission and reports the following findings:

1. This product is produced from an integrated formulation process as indicated by intended chemical reactions.
2. The impurity profile has changed slightly. See the confidential appendix for details.

3. The nominal concentration of the active ingredient listed on the revised basic and alternate CSFs and the label are the same.
4. The active ingredient's certified limits as proposed on the basic CSF are acceptable.

CONCLUSIONS:

TRB has reviewed this submission and concludes the following:

1. The revised basic and alternate formulation CSFs for the manufacturing use product, Emamectin Benzoate Technical both dated 05 Nov 2002 are acceptable.
2. This submission satisfies the data requirements as specified in 40 CFR 158.155, 158.160, 158.165, 158.167, 158.175, and 158.180 with respect to product identity and composition, description of materials used to produce the product, description of formulation process, discussion of formation of impurities, certified limits, and enforcement analytical method.

PRODUCT CHEMISTRY DATA (GROUP A)

| 21. <u>Chemical IDs/Manufacture/ Analytical Information</u> | <u>Data Required Fulfilled</u> | <u>MRID No.</u> |
|--|---|------------------------|
| 830-1550 Product Identity and Composition | Y | 460449-01 454208-01 |
| 830-1600 Description of Materials Used to Produce the Product | | see 454208-01 |
| 830-1620 Description of Production Process | | see 454208-01 |
| 830-1650 Description of Formulation Process | NA | |
| 830-1670 Discussion of Impurities | Y | 460449-01 454208-01 |
| 830-1700 Preliminary Analysis | Y | 460449-01 454208-01 |
| 830-1750 Certified Limits | Y | 460449-01 |
| 830-1800 Enforcement Analytical Method | Y | 460449-01 454208-01 |

Enforcement analytical method: (MRID No.460449-01)

The active ingredient and impurities were determined simultaneously by High Performance Liquid Chromatography (HPLC) with UV detection (245 nm) using external standard by Analytical method AW-212/1 and AK-212/2.

Equipment and ParametersAW-212/1

HPLC: Merck LaChrom L7100 (Merck Hitachi)

Detector: Merck LaChrom L7400 (Merck Hitachi); layer thickness: 8mm

Wavelength: 245 nm

Integrator: HPLC-Manager

Column: Inertsil C8, 250 mm x 4.6 mm id, 5 μ m

Column temperature: Room Temperature

Size of sample: 10 μ L

Mobile Phase: Acetonitrile/0.1% aqueous trifluoroacetic acid

Flow rate: 1.0 ml / min.

Duration of time: approximately 45 minutes

Retention time: MK 244 (NOA 422390)- 16.1 min. and MK 244 (NOA 426007)- 18.1 min.

| Gradient Program | Time(min) | ACN | 0.1% TEAA |
|------------------|-----------|-----|-----------|
| | 0 | 40 | 60 |
| | 20 | 55 | 45 |
| | 30 | 100 | 0 |
| | 35 | 100 | 0 |
| | 36 | 40 | 60 |
| | 45 | 40 | 60 |

AK-212/2

HPLC: Merck LaChrom L7100 (Merck Hitachi)

Detector: Merck LaChrom L7400 (Merck Hitachi); layer thickness: 8mm

Wavelength: 245 nm

Integrator: HPLC-Manager

Column: Kromasil 100-C8, 250 mm x 4.6 mm id, 3.5 μ m

Column temperature: Room Temperature

Size of sample: 10 μ L

Mobile Phase: Acetonitrile

Flow rate: 1.0 ml/min.

Duration of time: approximately 74 minutes

5

| Gradient Program | <u>Time(min)</u> | <u>10% borax</u> buffer sol. in water pH9 | <u>MeOH</u> | <u>ACN</u> |
|------------------|------------------|---|-------------|------------|
| | 0 | 50 | 0 | 50 |
| | 15 | 40 | 5 | 55 |
| | 20 | 30 | 15 | 55 |
| | 35 | 25 | 50 | 25 |
| | 50 | 20 | 35 | 45 |
| | 60 | 10 | 40 | 50 |
| | 65 | 10 | 40 | 50 |
| | 66 | 50 | 0 | 50 |
| | 74 | 50 | 0 | 50 |

CONFIDENTIAL APPENDIX

EP [x] MP [] PRODUCT CHEMISTRY REVIEW

BARCODE No.: D299038 REG./File Symbol No.: 100-902

PRODUCT NAME: Emamectin Benzoate Technical

Reviewer: BKitchens Company: Syngenta Crop Protection, Inc.





UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

August 6, 2003

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SYNGENTA CROP PROTECTION, INC
PO Box 18300
GREENSBORO, NC 27419-8300

Report of Analysis for Compliance with PR Notice 86-5

Thank you for your submittal of 24-JUL-03. Our staff has completed a preliminary analysis of the material. The results are provided as follows:

Your submittal was found to be in full compliance with the standards for submission of data contained in PR Notice 86-5. A copy of your bibliography is enclosed, annotated with Master Record ID's (MRIDs) assigned to each document submitted. Please use these numbers in all future references to these documents. Thank you for your cooperation. If you have any questions concerning this data submission, please raise them with the cognizant Product Manager, to whom the data have been released.



Syngenta Crop Protection, Inc. Tel 336 632 6000
Syngenta Crop Protection, Inc Tel 336 632 6000
P.O. Box 18300 Greensboro, NC 27419-8300
Greensboro, NC 27419-8300

NP-60449-00

Carolyn F. Brinkley
Sr. Regulatory Product Manager
Syngenta Crop Protection, Inc
Phone: (336) 632-2838
Fax: (336) 292-6374
E-mail: carolyn.brinkley@syngenta.com

Confidential

July 21, 2003

Document Processing Desk [AMEND]
Office of Pesticide Programs (7504C)
U.S. Environmental Protection Agency
Ariel Rios Building
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460

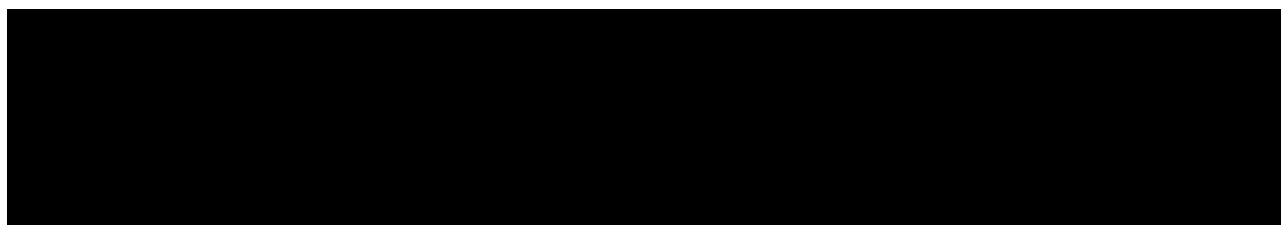
Attention: Mr. Thomas Harris
Insecticide-Rodenticide Branch

**SUBJECT: EMAMECTIN BENZOATE TECHNICAL
EPA REG. NO. 100-902
NEW SPECIFICATIONS BASED ON FULL-SCALE PRODUCTION IN
SWITZERLAND**

Gentlemen:

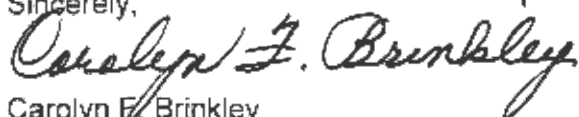
In 2001 Syngenta Crop Protection, Inc. submitted a revised basic and alternate confidential statement of formula and supporting product chemistry data for Emamectin Benzoate Technical, EPA Reg. No. 100-902. The purpose of the revision was to change the production location from the United States to Switzerland. The data that were submitted in 2001 were based on pilot scale production data. Now that full-scale production for Emamectin Technical has been ongoing in Switzerland for approximately one year the preliminary analysis, by-products and certified limits for emamectin benzoate have been refined. Therefore, Syngenta is submitting an addendum to the product chemistry data submitted to the EPA in 2001 (EPA MRID No. 45420801) and a revised basic and alternate confidential statement of formula for Emamectin Benzoate Technical.

Because the specifications of Emamectin Benzoate Technical are confidential, please consider the information in this letter and the accompanying data CBI. The changes are summarized as follows:



The attached Data Sheet explains these changes in greater detail. If you have any questions about these revisions, please contact me. I can be reached at (336) 632 2838.

Sincerely,



Carolyn E. Brinkley
Sr. Regulatory Product Manager
Regulatory Affairs

Enclosures: Volume 1 of 2 – Transmittal Document
Volume 2 of 2 – Manufacturing Process Description and Supporting Data for
Emamectin Benzoate Technical (Addendum to MRID
45420801)

**VOLUME 1 OF 2 OF SUBMISSION
(TRANSMITTAL DOCUMENT)**

1. Name and Address of Submitter

Syngenta Crop Protection, Inc.
P.O. Box 18300
Greensboro, NC 27419

2. Regulatory Action in Support of which this Package is Submitted

Enamectin Benzoate Technical New Specifications Based on Full-Scale Production in
Switzerland

3. Transmittal Date

07/22/2003

4. List of Submitted Studies

| MRID NUMBER | VOLUME NUMBER | STUDY TITLE | EPA GUIDELINE NUMBER |
|----------------|------------------|---|---|
| | 1 of 2 | Transmittal Document | Not Applicable |
| 45420801 | 2 of 2 | Manufacturing Process Description and Supporting Data for Enamectin Benzoate Technical (Addendum to MRID 45420801) (1543, 414774, PC-02-075) | 830.1550, 830.1700, 830.1750, 830.1800 |

Company Official: Carolyn F. Brinkley
(Name)

Carolyn F. Brinkley
(Signature)

Company Name: SYNGENTA CROP PROTECTION, INC.

Company Contact: Carolyn F. Brinkley
(Name)

336-632-2838
(Phone)



United States
Environmental Protection Agency
 Washington, DC 20460

☐ Registration
☒ Amendment
☐ Other

OPP Identifier Number
292923

Application for Pesticide - Section I

| | | |
|---|---|--|
| 1. Company/Product Number 100-902 | 2. EPA Product Manager Mr. Thomas Harris | 3. Proposed Classification <input checked="" type="checkbox"/> None <input type="checkbox"/> Restricted |
| 4. Company/Product (Name) Emamectin Benzoate Technical | PM# Insecticide/Rodenticide Branch | |
| 5. Name and Address of Applicant (Include ZIP Code) Syngenta Crop Protection, Inc. P. O. Box 18300 Greensboro, NC 27419 <input type="checkbox"/> Check if this is a new address | 6. Expedited Review. In accordance with FIFRA Section 3(c)(3) (b)(i), my product is similar or identical in composition and labeling to: EPA Reg. No. _____ Product Name _____ | |

Section - II

- ☒ Amendment - Explain below. ☐ Final printed labels in response to Agency letter dated _____
- ☐ Resubmission in response to Agency letter dated _____ ☐ "Me Too" Application.
- ☐ Notification - Explain below. ☐ Other - Explain below.

Explanation: Use additional page(s) if necessary. (For Section I and Section II.) The production of this technical was moved from the United States to Switzerland. Product chemistry data submitted to the EPA in 2001 were based on pilot scale production. Improvements in manufacturing at production scale level resulted in a need to change the levels of certain by-products. The accompanying product chemistry data support the revised confidential statements of formula (basic and alternate).

Section - III

| | | | | | |
|--|---|--|--|---|--|
| 1. Material This Product Will Be Packaged In: | | | | | |
| Child-Resistant Packaging <input type="checkbox"/> Yes* <input type="checkbox"/> No | Unit Packaging <input type="checkbox"/> Yes <input type="checkbox"/> No | Water Soluble Packaging <input type="checkbox"/> Yes <input type="checkbox"/> No | 2. Type of Container <input type="checkbox"/> Metal <input type="checkbox"/> Plastic <input type="checkbox"/> Glass <input type="checkbox"/> Paper <input type="checkbox"/> Other (Specify) _____ | | |
| *Certification must be submitted | | If "Yes" Unit Packaging wgt. No. per container | If "Yes" Unit Packaging wgt. No. per container | | |
| 3. Location of Net Contents Information <input type="checkbox"/> Label <input type="checkbox"/> Container | | 4. Size(s) Retail Container | | 5. Location of Label Directions <input type="checkbox"/> On Label <input type="checkbox"/> On Labeling accompanying product | |
| 6. Manner in Which Label is Affixed to Product <input type="checkbox"/> Lithograph <input type="checkbox"/> Other _____ <input type="checkbox"/> Paper glued <input type="checkbox"/> Stenciled | | | | | |

Section - IV

| | | | | | |
|--|--|---|--|---|--|
| 1. Contact Point (Complete items directly below for identification of individual to be contacted, if necessary, to process this application.) | | | | | |
| Name Carolyn F. Brinkley | | Title Senior Regulatory Product Manager | | Telephone No. (Include Area Code) (336) 632-2838 | |
| Certification I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law. | | | | | 6. Date Application Received (Stamped) |
| 2. Signature <i>Carolyn F. Brinkley</i> | | 3. Title Senior Regulatory Product Manager | | | |
| 4. Typed Name Carolyn F. Brinkley | | 5. Date July 21, 2003 | | | |

EPA Form 8570-1 (Rev. 8-94) Previous editions are obsolete.



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

April 14, 2004

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

PLEASE RETURN A COPY OF THIS LETTER WITH PAYMENT

OPP Decision Number: D-339531
EPA File Symbol or Registration Number: 100-902
Product Name: EMAMECTIN BENZOATE TECHNICAL
EPA Receipt Date: 24-Jul-2003
EPA Company Number: 100
Company Name: SYNGENTA CROP PROTECTION, INC.

CAROLYN BRINKLEY
SYNGENTA CROP PROTECTION, INC.
ATTN: REGULATORY AFFAIRS
PO Box 18300
GREENSBORO, NC 27419-8300

SUBJECT: Receipt of Registration Service Fee Voluntary Payment Notice

Dear Registrant:

The Office of Pesticide Programs has received your Notice of Intent to Submit Voluntary Payment for the action described below.

The Action has been identified as Action Code: R34

NON-FAST-TRACK (INCLUDES CHANGES TO PRECAUTIONARY LABEL
STATEMENTS; SOURCE CHANGES TO AN UNREGISTERED SOURCE):

The net amount due was calculated by determining the fee associated with this action (from the March 17, 2004 Federal Register Notice), calculating the amount of work that has been completed on the particular action, and reducing the basic fee by the appropriate percentage of work completed. This amount was further reduced by the amount of any tolerance fee paid in association with this action if applicable.

You may be eligible for a full or partial waiver of the fee. Refer to OPP's Fee for Service web site at www.epa.gov/pesticides/fees for guidance on how to request a waiver.

Please remit payment in the amount of: \$ 2,700 to:

By USPS:

USEPA Washington Finance Center
Pesticide Registration Service Fee
PO Box 360277
Pittsburgh, PA 15251

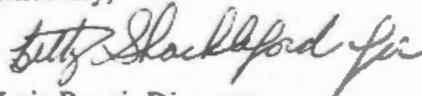
By Courier:

U.S. EPA Washington Finance Center
Pesticide Registration Service Fee
C/O Mellon Client Service Center
500 Ross Street, Room 670
Box 360277
Pittsburgh, PA 15251-6277
Attn: EPA Module Supervisor

All payments must be in United States currency by check, bank draft, or money order drawn to the order of the Environmental Protection Agency. To ensure proper credit, please write the OPP DECISION NUMBER on your check, and enclose a copy of this letter with your payment.

If you have any questions, please contact the Pesticide Registration Service Fee Ombudsman at (703) 305-6249.

Sincerely,



Lois Rossi, Director
Registration Division

FEE FOR SERVICE

DIVISION: RD

PRODUCT /RISK MANAGER: 7

EPA FILE SYMBOL/REG. NO.: 100-902

D 339531

5754810

DP299038

PIN-PUNCH DATE: 3/26/04

ACTION CODE: R34 (per Syngenta)

AMOUNT DUE: Syngenta willing to pay
~~\$3,000~~ \$2700

WAIVER REQUEST ☒ No

- ☐ Small Business 100%
- ☐ Small Business 50%
- ☐ IR4
- ☐ Minor Use
- ☐ Federal/State

Action code = R34

Fee = \$3,000

- 10%

\$2,700

REVIEWER: J. Bazuin

REMARKS: VOLPAY

prod chem sent to TRB 2/23/04, due ^{back} 4/8/04

MWaws

Receipt for Section 3

S: 757053

Regulatory Type: Product Registration - Section 3

Relationship: ☐ Yes ☒ No

Print Letter

Application Type: Voluntary Fee Payment

Fee For Service: ☒ Yes ☐ No

Enter More Information

Company: 100 SYNGENTA CROP PROTECTION, INC.

V

Risk Manager: Registration Division, Risk Management Team 7

Product #: 100-903

Product Name: EMAMECTIN BENZOATE TECHNICAL

Me Too
Section 3

Me Too
Product Name:

Application Date: 23-Mar-2004

lic

OPP Rec'd Date: 26-Mar-2004

lic

Receipt Content

Front End Date: 26-Mar-2004

lic

Risk Manager Send Date: 29-Mar-2004

lic

Fast Track

☐

New Ingredient

☐

Receipt Description:

New Ingredient
Request Date

New Ingredient
Received Date

Form 3

☐

Signature Date

Form 3

☐

Signature Date



United States
Environmental Protection Agency
Washington, DC 20460

☐ Registration
☐ Amendment
☒ Other

OPP Identifier Number

Application for Pesticide - Section I

| | | |
|---|---|--|
| 1. Company/Product Number 100-902 | 2. EPA Product Manager John Hebert | 3. Proposed Classification <input checked="" type="checkbox"/> None <input type="checkbox"/> Restricted |
| 4. Company/Product (Name) Enamectin Benzoate | PM# 4 | |
| 5. Name and Address of Applicant (include ZIP Code) Syngenta Crop Protection, Inc. P. O. Box 18300 Greensboro, NC 27419 <input type="checkbox"/> Check if this is a new address | 6. Expedited Review. In accordance with FIFRA Section 3(c)(3) (b)(i), my product is similar or identical in composition and labeling to: EPA Reg. No. _____ Product Name _____ | |

Section - II

- ☐ Amendment - Explain below. ☐ Final printed labels in response to Agency letter dated _____
- ☐ Resubmission in response to Agency letter dated _____ ☐ "Me Too" Application. _____
- ☐ Notification - Explain below. ☒ Other - Explain below. _____

Explanation: Use additional page(s) if necessary. (For Section I and Section II.)

VOLPAY

Offering Voluntary Fee Payment under PRIA for Enamectin Benzoate (EPA reg # 100-902) requesting approval of a new production site. Submitted 7/29/2003.

R34/89; \$3,000

E-mail: Carolyn.Brinkley@syngenta.com

Fax: 1-336-292-6374

Section - III

| | | | | | |
|---|---|--|--|---|--|
| 1. Material This Product Will Be Packaged In: | | | | 2. Type of Container | |
| Child-Resistant Packaging <input type="checkbox"/> Yes* <input type="checkbox"/> No | Unit Packaging <input type="checkbox"/> Yes <input type="checkbox"/> No | Water Soluble Packaging <input type="checkbox"/> Yes <input type="checkbox"/> No | <input type="checkbox"/> Metal <input type="checkbox"/> Plastic <input type="checkbox"/> Glass <input type="checkbox"/> Paper <input type="checkbox"/> Other (Specify) _____ | | |
| *Certification must be submitted | | If "Yes" Unit Packaging wgt. No. per container | If "Yes" Unit Packaging wgt. No. per container | | |
| 3. Location of Net Contents Information <input type="checkbox"/> Label <input type="checkbox"/> Container | | 4. Size(s) Retail Container | | 5. Location of Label Directions <input type="checkbox"/> On Label <input type="checkbox"/> On Labeling accompanying product | |
| 6. Manner in Which Label is Affixed to Product <input type="checkbox"/> Lithograph <input type="checkbox"/> Paper glued <input type="checkbox"/> Stenciled <input type="checkbox"/> Other _____ | | | | | |

Section - IV

| | | | |
|--|--|---|--|
| 1. Contact Point (Complete items directly below for identification of individual to be contacted, if necessary, to process this application.) | | | |
| Name Carolyn F. Brinkley | | Title Senior Regulatory Product Manager Phone 1-336-632-2838 | |
| Certification I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment of both under applicable law. | | | |
| 2. Signature | | 3. Title Senior Regulatory Product Manager | |
| 4. Typed Name Carolyn F. Brinkley | | 5. Date 3/23/2004 | |
| 6. Date Application Received (Stamped) | | | |

EPA Form 8570-1 (Rev. 8-94) Previous editions are obsolete.



U.S. ENVIRONMENTAL PROTECTION AGENCY
Office of Pesticide Programs
Registration Division (7505C)
1200 Pennsylvania Ave., NW
Washington, D.C. 20460

EPA Reg. Number:

100-902

Date of

3/30/04

Term of Issuance:

Conditional, extended until
5/1/05

Name of Pesticide Product:

Emamectin Benzoate
Technical

NOTICE OF PESTICIDE:

x Registration

(under FIFRA, as amended) Reregistration

Name and Address of Registrant (include ZIP Code):

Carolyn Brinkley
Syngenta Crop Protection, Inc.
PO Box 18300
Greensboro, NC 27419

Note: Changes in labeling differing in substance from that accepted in connection with this registration must be submitted to and accepted by the Registration Division prior to use of the label in commerce. In any correspondence on this product always refer to the above EPA registration number.

On the basis of information furnished by the registrant, the above named pesticide is hereby registered/reregistered under the Federal Insecticide, Fungicide and Rodenticide Act.

Registration is in no way to be construed as an endorsement or recommendation of this product by the Agency. In order to protect health and the environment, the Administrator, on his motion, may at any time suspend or cancel the registration of a pesticide in accordance with the Act. The acceptance of any name in connection with the registration of a product under this Act is not to be construed as giving the registrant a right to exclusive use of the name or to its use if it has been covered by others.

The above product was conditionally registered on 5/19/99 with an expiration date of 5/1/02. The registration was extended on 4/19/02 by EPA until 5/1/03 and again on 4/18/03 until 5/1/04. This letter serves to extend the conditional registration expiration date for this product an additional year, i.e. until 5/1/05.

This time extension will allow for review of an estuarine/marine invertebrate life-cycle study (guideline OPP 72-4b = OPPTS 850.1350) which was noted as a condition of registration for end use products EPA Registration # 100-903 and # 100-904. After the EPA denial of a Syngenta waiver request the registrant agreed to run the study. The study was submitted on 1/7/03, assigned MRID 458330-01, and is currently in review.

Signature of Approving Official:

Thomas C. Harris, Biologist
Insecticide-Rodenticide Branch
Registration Division (7504C)

Date:

3/30/04



Thomas Harris

03/30/2004 01:56 PM

To: Stephanie Syslo/DC/USEPA/US@EPA
cc: Ben Smith/DC/USEPA/US@EPA, Stephanie
Syslo/DC/USEPA/US@EPA, Thuy Nguyen/DC/USEPA/US@EPA
Subject: Re: emamectin - estuar/marine invert study

No problem. I'll extend the registrations for another year to 5/1/05.

Trying to remember that there is an expiration date is a bit of a problem. We're trying to get a field added in OPPIN to track this sort of thing. Some time before the registration is set to expire it should start flashing red, making noise, and generally reminding us to take care of it. It can cause a huge legal mess if we forget and the registration expires (it happened once in our branch).

So . . . if EFED could just get the review done by the end of the calendar year (well in advance of when the expiration comes up again) it would be great. In addition, I'll put a note on my calendar to remind you next February if it's not done. Actually, this might be a good study to give a new hire since I expect the results are just confirmatory.

Tom Harris
EPA/OPPTS/OPP/RD/IRB
(703) 308-9423
harris.thomas@epa.gov
visit <http://www.epa.gov/pesticides>
Stephanie Syslo



Stephanie Syslo
Sent by: Stephanie Syslo

03/30/2004 09:40 AM

To: Thomas Harris/DC/USEPA/US@EPA
cc: Thuy Nguyen/DC/USEPA/US@EPA, Ben Smith/DC/USEPA/US@EPA
Subject: Re: emamectin - estuar/marine invert study

Tom,

I know you asked Thuy the question, but since this is a scheduling issue, I need to chime in. ERB 3 doesn't have a biologist assigned to this chemical, and we're way short on biologists right now. So, there is no way we can get the review done for you by mid-April. Sorry.

Just interested: Is the extension just for a year? If so and if it does not cause problems for you, could you please nudge us again about 3 months before the registration expires, so we can get it done for you? We'll be in better shape after we get all our biologists on board and trained. Thanks.

Steph
305-6355
Thuy Nguyen/DC/USEPA/US@EPA



Thuy
Nguyen/DC/USEPA/US
@EPA

03/29/1993 08:59 PM

To: Stephanie Syslo/DC/USEPA/US@EPA
cc:
Subject: emamectin - estuar/marine invert study



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

February 23, 2004

Carolyn Brinkley
Syngenta Crop Protection, Inc.
PO Box 18300
Greensboro, NC 27419

Subject: Enamectin Technical, EPA Reg. # 100-902
label amendment submitted 8/29/03
accepted with comments

Dear Ms. Brinkley,

The revised labeling reference to above, submitted in connection with the registration under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended, is acceptable provided you incorporate the changes required by the Agency as listed below.

| Topic | Action required |
|---------------------------------|--|
| Directions for Use site list | EXPAND the term "turnip greens" to "turnip greens (tops, leaves)". ADD a footnote to the new term turnip greens (tops, leaves) term that reads: "Turnip Greens (tops, leaves) only: For use on turnip varieties grown for leaves only. Do not use on turnip varieties grown for roots or dual-purpose varieties grown for roots and leaves." [this is text is from 100-904] |

Submit two (2) copies of your final printed labeling incorporating the above changes prior to releasing your product for shipment. If the above provisions are not complied with the registration will be subject to cancellation in accordance with

FIFRA Section 6(e). Your release for shipment of the product bearing the amended labeling constitutes acceptance of these conditions.

A copy of your label stamped "accepted with comments" is enclosed for your records.

If you have any questions please contact me at (703) 308-9423 or Harris.Thomas@EPA.gov.

Sincerely yours,



Thomas C. Harris
Insecticide / Rodenticide Branch
Registration Division (7505C)
Office of Pesticide Programs

enclosure

Eamectin Benzoate Technical

An insecticide for formulation into end-use insecticide products intended for non-domestic terrestrial outdoor food use.

| | |
|--|--------|
| Active Ingredient: | |
| Eamectin Benzoate (CAS No. 155569-91-8)..... | 97.0% |
| Other Ingredients: | 3.0% |
| Total: | 100.0% |

KEEP OUT OF REACH OF CHILDREN

DANGER/PELIGRO

Si usted no entiende la etiqueta, busque a alguien para que se la explique a usted en detalle. (If you do not understand the label, find someone to explain it to you in detail.)

See additional precautionary statements on label.

EPA Reg. No. 100-902
EPA Est.

Product ID.

Product of Switzerland

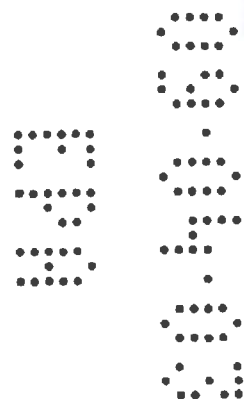
SCP 902A-L(Draft C)

Net Contents

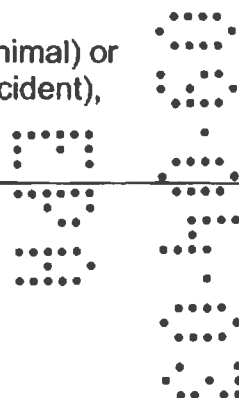
ACCEPTED
with COMMENTS
in EPA Letter Dated:
FEB 23 2004

Under the Federal Insecticide,
Fungicide, and Rodenticide Act
as amended, for the pesticide
registered under EPA Reg. No.

100-902



| FIRST AID | |
|--|---|
| If in eyes | <ul style="list-style-type: none"> • Hold eye open and rinse slowly and gently with water for 15-20 minutes. • Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. • Call a poison control center or doctor for treatment advice. |
| If swallowed | <ul style="list-style-type: none"> • Call a poison control center or doctor immediately for treatment advice. • Have person sip glass of water if able to swallow. • Do not induce vomiting unless told to do so by a poison control center or doctor. • Do not give anything by mouth to an unconscious person |
| If on skin or clothing | <ul style="list-style-type: none"> • Take off contaminated clothing. • Rinse skin immediately with plenty of water for 15-20 minutes. • Call a poison control center or doctor for treatment advice. |
| If inhaled | <ul style="list-style-type: none"> • Move person to fresh air. • If person is not breathing, call 911 or an ambulance, and then give artificial respiration, preferably mouth-to-mouth, if possible. • Call a poison control center or doctor for treatment advice. |
| <p align="center">NOTE TO PHYSICIAN</p> <p>Probably mucosal damage may contraindicate the use of gastric lavage. Early signs of intoxication include dilated pupils, muscular incoordination, and muscle tremors. If toxicity from exposure has progressed to cause severe vomiting, the extent of resultant fluid and electrolyte imbalance should be gauged. Appropriate supportive parenteral fluid replacement therapy should be given, along with other required supportive measures (such as maintenance of blood pressure levels and proper respiratory functionality) as indicated by clinical signs, symptoms, and measurements.</p> <p>In severe cases, observations should continue for at least several days until clinical condition is stable and normal. Since emamectin benzoate is believed to enhance GABA activity in animals, it is probably wise to avoid drugs that enhance GABA activity (barbiturates, benzodiazepines, valproic acid) in patients with potentially toxic emamectin benzoate exposure.</p> <p>Have the product container or label with you when calling a poison control center or doctor, or going for treatment.</p> | |
| <p align="center">HOT LINE NUMBER</p> <p align="center">For 24 Hour Medical Emergency Assistance (Human or Animal) or Chemical Emergency Assistance (Spill, Leak, Fire, or Accident), Call 1-800-888-8372</p> | |



PRECAUTIONARY STATEMENTS

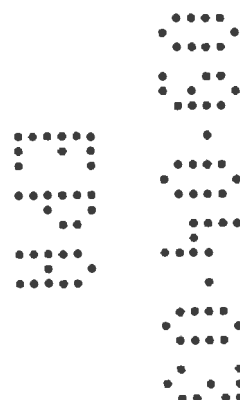
Hazards to Humans and Domestic Animals

Danger/Peligro

Corrosive. Causes irreversible eye damage. Do not get in eyes or on clothing. Wear protective eyewear (goggles, face shield, or safety glasses). May be fatal if swallowed. Wash thoroughly with soap and water after handling and before eating, drinking, or using tobacco. Remove and wash contaminated clothing before reuse.

Environmental Hazards

This pesticide is toxic to fish, birds, mammals, and aquatic invertebrates. Do not discharge effluent containing this active ingredient into lakes, streams, ponds, estuaries, oceans, or other public waters, unless in accordance with the requirements of a National Pollutant Discharge Elimination System (NPDES) permit, and the permitting authority has been notified in writing prior to discharge. Do not discharge effluent containing this product into sewer systems without previously notifying the local sewage treatment plant authority. For guidance, contact your State Water Board or Regional Office of the EPA.



CONDITIONS OF SALE AND LIMITATION OF WARRANTY AND LIABILITY

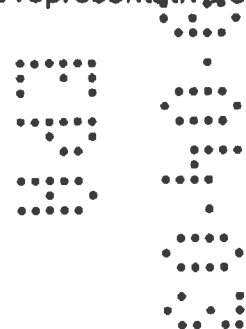
NOTICE: Read the entire Directions for Use and Conditions of Sale and Limitation of Warranty and Liability before buying or using this product. If the terms are not acceptable, return the product at once, unopened, and the purchase price will be refunded.

The Directions for Use of this product should be followed carefully. It is impossible to eliminate all risks inherently associated with the use of this product. Crop injury, ineffectiveness or other unintended consequences may result because of such factors as manner of use or application, weather or crop conditions, presence of other materials or other influencing factors in the use of the product, which are beyond the control of SYNGENTA CROP PROTECTION, Inc. or Seller. All such risks shall be assumed by Buyer and User, and Buyer and User agree to hold SYNGENTA and Seller harmless for any claims relating to such factors.

SYNGENTA warrants that this product conforms to the chemical description on the label and is reasonably fit for the purposes stated in the Directions for Use, subject to the inherent risks referred to above, when used in accordance with directions under normal use conditions. This warranty does not extend to the use of the product contrary to label instructions, or under abnormal conditions or under conditions not reasonably foreseeable to or beyond the control of Seller or SYNGENTA, and Buyer and User assume the risk of any such use. SYNGENTA MAKES NO WARRANTIES OF MERCHANTABILITY OR OF FITNESS FOR A PARTICULAR PURPOSE NOR ANY OTHER EXPRESS OR IMPLIED WARRANTY EXCEPT AS STATED ABOVE.

In no event shall SYNGENTA or Seller be liable for any incidental, consequential or special damages resulting from the use or handling of this product. **THE EXCLUSIVE REMEDY OF THE USER OR BUYER, AND THE EXCLUSIVE LIABILITY OF SYNGENTA AND SELLER FOR ANY AND ALL CLAIMS, LOSSES, INJURIES OR DAMAGES (INCLUDING CLAIMS BASED ON BREACH OF WARRANTY, CONTRACT, NEGLIGENCE, TORT, STRICT LIABILITY OR OTHERWISE) RESULTING FROM THE USE OR HANDLING OF THIS PRODUCT, SHALL BE THE RETURN OF THE PURCHASE PRICE OF THE PRODUCT OR, AT THE ELECTION OF SYNGENTA OR SELLER, THE REPLACEMENT OF THE PRODUCT.**

SYNGENTA and Seller offer this product, and Buyer and User accept it, subject to the foregoing Conditions of Sale and Limitation of Warranty and of Liability, which may not be modified except by written agreement signed by a duly authorized representative of SYNGENTA.



DIRECTIONS FOR USE

It is a violation of Federal law to use this product in a manner inconsistent with its labeling.

This product may be used only for the formulation of end-use insecticide products registered by the EPA for use on leafy vegetables, including *Brassica*, turnip greens, fruiting vegetables, cotton, and tobacco.

STORAGE AND DISPOSAL

Do not contaminate water, food, or feed by storage or disposal.

Pesticide Storage

Store in a tightly closed original container in a cool, dry place. Do not store near food or feed.

Pesticide Disposal

Pesticide wastes are acutely hazardous. Improper disposal of excess pesticide, or rinsate is a violation of Federal law. If these wastes cannot be disposed of by use according to label instructions, contact your State Pesticide or Environmental Control Agency, or the Hazardous Waste representative at the nearest EPA Regional Office for guidance. Pesticide that cannot be used or chemically reprocessed must be disposed of according to federal, state, or local procedures under the Resource Conservation and Recovery Act.

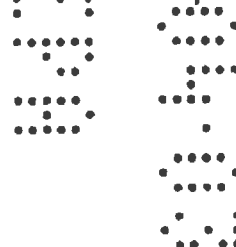
Container Disposal

Bulk

Thoroughly clean container before reuse. Consult Federal, state, or local disposal authorities for approved alternative procedures.

250 Gal. Mini Bulk

This is a refillable container that must be returned to an authorized Syngenta refilling facility for refilling or disposal. Before refilling, inspect thoroughly for damage such as cracks, punctures, bulges, dents, abrasions, and damaged or worn threads on closure devices. After filling and before transporting, check for leaks. Do not refill or transport damaged or leaking container.



Other Containers

Triple rinse (or equivalent). Then offer for recycling or reconditioning, or puncture and dispose of in a sanitary landfill, or by other procedures approved by state and local authorities.

CONTAINER IS NOT SAFE FOR FOOD, FEED, OR DRINKING WATER.

Note: For minor spills, leaks, etc. follow all precautions indicated on this label and clean up immediately. Take special care to avoid contamination of equipment and facilities during clean up and disposal of wastes.

Emamectin Benzoate Technical and the Syngenta logo are trademarks of a Syngenta Group Company.

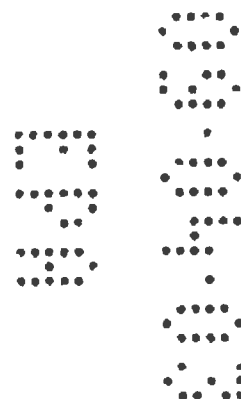
©2003 Syngenta

For non-emergency (e.g. current product information)
call Syngenta Crop Protection, Inc. at 1-800-334-9481

Syngenta Crop Protection, Inc.
Greensboro, North Carolina 27409
www.syngenta-us.com

SCP 902A-L(Draft C)

EMA BEN TEC 902A-L(Draft C)clean-lg-8-20-03 000100-00902.20030820.c.PDF

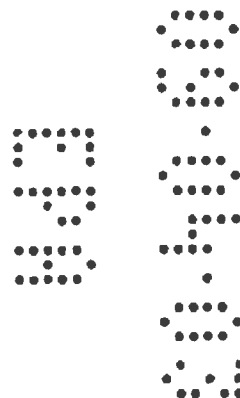


Chron

August 30, 2001 – draft revised label to EPA, revised first aid statements according to PR Notice 2001-1, revised ingredient statement according to new CSF and prod. chem, revised and added storage and disposal statements, specified on front panel end-use product uses supported for this active ingredient. Corrected label by adding Spanish signal word and warning statement, deleted chemical name of active – common name and CAS no. are sufficient, changed all references to Novartis to Syngenta and replaced Warranty statement with new Syngenta Warranty Statement, changed country of origin to Switzerland, revised ingredient statement per PR Notices 97-5 & 97-6

July 31, 2003 – In July, EPA set new tolerances for emamectin: leafy vegs crop group, Brassica leafy vegs group, turnip tops, cotton and EPA approved a new use on tobacco.

August 20, 2003 – Draft – Added new approved uses, deleted Skull and Crossbones and "Poison", revised order of First Aid statement, made minor non-notif changes.





UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

September 9, 2003

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

KAREN V. TRIPP
SYNGENTA CROP PROTECTION, INC.
PO Box 18300
GREENSBORO, NC 27419-8300

PRODUCT NAME: EMAMECTIN BENZOATE TECHNICAL
COMPANY NAME: SYNGENTA CROP PROTECTION, INC.
OPP IDENTIFICATION NUMBER: 292929
EPA FILE SYMBOL: 100-902
EPA RECEIPT DATE: 09/04/03

SUBJECT: RECEIPT OF AMENDMENT

DEAR REGISTRANT:

The Office of Pesticide Programs has received your application for an amendment and it has passed an administrative screen for completeness.

During the initial screen we determined that the application appears to qualify for fast track review. The package will now be forwarded to the Product Manager for review to determine its acceptability for fast track status.

If you have any questions, please contact Registration Division, Risk Management Team 1, at (703) 305-7546.

Sincerely,

A handwritten signature in cursive script, appearing to read "Jen".

Front End Processing Staff
Information Services Branch
Information Resources and Services Division



Carolyn F. Brinkley
Sr. Regulatory Product Manager
Regulatory Affairs
carolyn.brinkley@syngenta.com
(336) 632 2838

Syngenta Crop Protection, Inc.
P. O. Box 18300
410 Swing Road
Greensboro, NC 27419-8300

August 26, 2003

Document Processing Desk [AMEND]
Office of Pesticide Programs (7504C)
U.S. Environmental Protection Agency
Ariel Rios Building
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460

Attention: Mr. Thomas Harris, Insecticide-Rodenticide Branch

**SUBJECT: EMAMECTIN BENZOATE TECHNICAL
EPA REG. NO. 100-902
LABEL REVISION TO INCLUDE NEW END USES APPROVED 8/22/03**

Dear Sir or Madam:

On August 22, 2003 the EPA approved a revised labels for the emamectin-based end – use products, Proclaim® Insecticide and Denim Insecticide (EPA Reg. Nos. 100-904 & 100-903. These new uses included fruiting vegetables, leafy vegetables, Brassica vegetables, turnip greens, and cotton. As required by the EPA, Syngenta has revised the label for Emamectin Benzoate Technical to allow formulation of end-use insecticide products for these new uses. The revised label is attached and changes are marked on one copy to facilitate review. If you have any questions or comments about this label, please contact me. I can be reached at (336) 632-2838.

Sincerely yours,

Carolyn F. Brinkley
Sr. Regulatory Product Manager
Regulatory Affairs

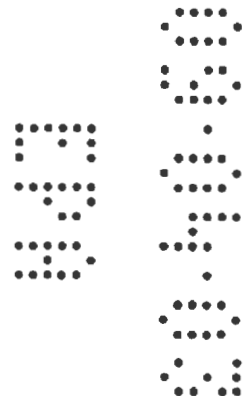
Enclosures: 5 copies of revised Emamectin Technical Label - one with revisions marked
1 copy of revised label on CD ROM
Certification with Respect to Label Integrity
EPA Application for Registration Form (8570-1)



bcc: R. Gold

RA file 100-902/Enamectin Technical/Label Revision (new uses approved 8/22/03) *+attaches*

K. Clark/Enamectin Technical Label Revision (new uses approved 8/22/03)



| | | | |
|---|--|--|--|
|  | United States Environmental Protection Agency Washington, DC 20460 | <input type="checkbox"/> Registration <input checked="" type="checkbox"/> Amendment <input type="checkbox"/> Other | OPP Identifier Number 292929 |
|---|--|--|--|

Application for Pesticide - Section I

| | | |
|---|---|--|
| 1. Company/Product Number 100-902 | 2. EPA Product Manager Mr. Thomas Harris | 3. Proposed Classification <input checked="" type="checkbox"/> None <input type="checkbox"/> Restricted |
| 4. Company/Product (Name) Emamectin Benzoate Technical | PM# Insecticide-Rodenticide Branch | |
| 5. Name and Address of Applicant (Include ZIP Code) Syngenta Crop Protection, Inc. P. O. Box 18300 Greensboro, NC 27419 <input type="checkbox"/> Check if this is a new address | 6. Expedited Review. In accordance with FIFRA Section 3(c)(3) (b)(i), my product is similar or identical in composition and labeling to: EPA Reg. No. _____ Product Name _____ | |

Section - II


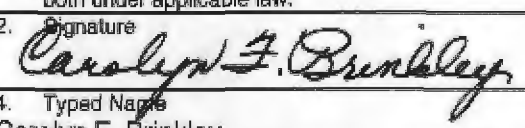

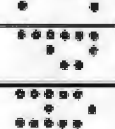
| | |
|--|---|
| <input checked="" type="checkbox"/> Amendment - Explain below. <input type="checkbox"/> Resubmission in response to Agency letter dated _____ <input type="checkbox"/> Notification - Explain below. | <input type="checkbox"/> Final printed labels in response to Agency letter dated _____ <input type="checkbox"/> "Me Too" Application. <input type="checkbox"/> Other - Explain below. |
|--|---|

Explanation: Use additional page(s) if necessary. (For Section I and Section II.) On August 22, 2003 EPA approved use on fruiting vegetables, leafy vegetables, *Brassica* leafy vegetables, turnip greens, and cotton. As required by the EPA, Syngenta has revised the Emamectin Benzoate Technical label to allow formulation into end-use products for these new uses.

Section - III

| | | | | | |
|--|---|--|---|--|--|
| 1. Material This Product Will Be Packaged In: | | | | 2. Type of Container <input type="checkbox"/> Metal <input type="checkbox"/> Plastic <input type="checkbox"/> Glass <input type="checkbox"/> Paper <input type="checkbox"/> Other (Specify) _____ | |
| Child-Resistant Packaging <input type="checkbox"/> Yes* <input type="checkbox"/> No | Unit Packaging <input type="checkbox"/> Yes <input type="checkbox"/> No | Water Soluble Packaging <input type="checkbox"/> Yes <input type="checkbox"/> No | | | |
| <i>*Certification must be submitted</i> | | If "Yes" Unit Packaging wgt. No. per container | If "Yes" Unit Packaging wgt. No. per container | | |
| 3. Location of Net Contents Information <input type="checkbox"/> Label <input type="checkbox"/> Container | | 4. Size(s) Retail Container | | 5. Location of Label Directions <input type="checkbox"/> On Label <input type="checkbox"/> On Labeling accompanying product | |
| 6. Manner in Which Label is Affixed to Product <input type="checkbox"/> Lithograph <input type="checkbox"/> Other _____ <input type="checkbox"/> Paper glued <input type="checkbox"/> Stenciled | | | | | |

Section - IV

| | | |
|--|---|---|
| 1. Contact Point (Complete items directly below for identification of individual to be contacted, if necessary, to process this application.) | | |
| Name Carolyn F. Brinkley | Title Senior Regulatory Product Manager | Telephone No. (Include Area Code) (336) 632-2838 |
| Certification I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law. | | 6. Date Application Received (Stamped) <div style="text-align: center;">  </div> |
| 2. Signature  | 3. Title Senior Regulatory Product Manager | <div style="text-align: center;">  </div> |
| 4. Typed Name Carolyn F. Brinkley | 5. Date August 29, 2003 | <div style="text-align: center;">  </div> |

EPA Form 8570-1 (Rev. 8-94) Previous editions are obsolete.

Certification with Respect to Label Integrity

Version: 9/11/02

I certify that the information (including, but not limited to, text, tables, and graphics) contained in the electronic file identified below by file name and submitted with this certification is the same information as that on the paper copies of these documents included with this submission.

| PROPOSED LABEL | | |
|--------------------|-----------------------|-----------------------------|
| EPA Registration # | Date Submitted to EPA | Electronic file name |
| 100-902 | August 29, 2003 | 000100-00902.20030820.c.PDF |

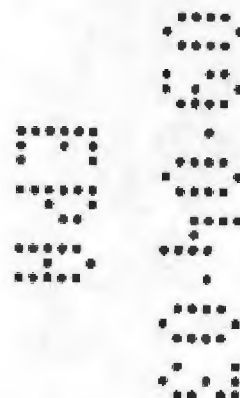
I certify that the statements that I have made on this form are true, accurate, and complete. I acknowledge that any knowingly false or misleading statements may be punishable by fine or imprisonment or both under applicable law.

Carolyn F. Brinkley
Signature

August 29, 2003
Date

Carolyn F. Brinkley
Name (typed)

Sr. Regulatory Product
Manager
Title





UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

February 5, 2004

I, John Hebert, Insecticide/Rodenticide Branch, Registration Division, Office of Pesticide Programs, Office of Prevention, Pesticides and Toxic Substances, United States Environmental Protection Agency ("EPA"), certify that the pesticide product(s) listed below is, as of the date of this letter, a registered product under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended, and that as such, the product(s) may be sold and marketed in the United States of America as authorized and limited by FIFRA. A true and correct copy of the product label approved by EPA is attached to accompany this letter.

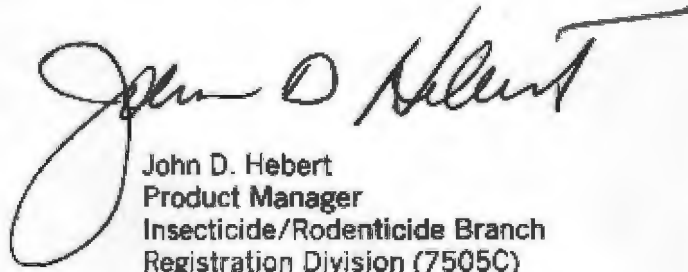
Registration of this product(s) with EPA also denotes that the registrant listed below is responsible for ensuring full compliance with all the laws of the United States of America, or governing jurisdiction, regarding the sale, storage and/or disposal of the product(s). Further, the recipient of this letter is on notice that the referenced registration and/or the accompanying label may change subsequent to the date of this letter. EPA assumes no responsibility to notify the recipient of this letter of any change in the status of the registration(s) and/or the product label for the product(s) listed below.

EPA has issued registration numbers for the product(s) listed below to:

Syngenta Crop Protection, Inc.
P.O. Box 18300
Greensboro, NC 27419-8300

EPA Registration Number:
Name of Product:

100-902
Enamectin Benzoate Technical


John D. Hebert
Product Manager
Insecticide/Rodenticide Branch
Registration Division (7505C)



Syngenta Crop Protection, Inc. Tel 336 632 6000
P.O. Box 18300
Greensboro, NC 27419-8300
www.syngenta.com



REQUEST BY FAX
Fax No. (703) 305-6596

January 21, 2004

Mr. Arnold Lane, Chief
Insecticide Branch, Registration Division
Office of Pesticide Programs (7505C)
U.S. Environmental Protection Agency
Ariel Rios Building
1200 Pennsylvania Ave. NW
Washington, DC 20460

Dear Mr. Lane:

SUBJECT: REQUEST FOR CERTIFICATES OF REGISTRATION

Our Syngenta colleagues in other countries to whom Syngenta Crop Protection, Inc. U.S. supplies product, require Certificates of Registration (gold seals) for those products to satisfy their individual country's registration requirements. Please provide us with three Certificates of Registration for the following product(s):

| <u>Name of Product</u> | <u>EPA Reg. No.</u> |
|------------------------------|---------------------|
| EMAMECTIN BENZOATE Technical | 100-902 |
| PROCLAIM Insecticide | 100-904 |

To meet the registration timelines in the requesting countries, please provide the Certificates of Registration as soon as possible. If you have any questions about this request, please contact me at the below telephone number. Thank you for your time and assistance.

Sincerely,

Kathleen M. Campbell

Kathy Campbell
Staff Quality Assurance Auditor
Regulatory Affairs
PH 336-632-7672

APR 10 2003

U.S. ENVIRONMENTAL PROTECTION AGENCY
Office of Pesticide Programs

SYNGENTA CROP PROTECTION, INC.
P.O. BOX 18300
GREENSBORO, NC 274198300

Report of Analysis for Compliance with PR Notice 86-5

Thank you for your transmittal of 04/02/03. Our staff has completed a preliminary analysis of the material. The results are provided as follows:

Your submittal was found to be in full compliance with the standards for submission of data contained in PR Notice 86-5. A copy of your bibliography is enclosed, annotated with Master Record ID's (MRIDs) assigned to each document submitted. Please use these numbers in all future references to these documents. Thank you for your cooperation. If you have any questions concerning this data submission, please raise them with the cognizant Product Manager, to whom the data have been released.



March 28, 2003

Document Processing Desk (AMEND)
Office of Pesticide Programs (7504C)
U.S. Environmental Protection Agency
401 M Street S.W.
Washington, DC 20460

3F6574

Attention: Mr. Thomas Harris, Insecticides Rodenticides Branch

**SUBJECT: EMAMECTIN BENZOATE TECHNICAL, EPA REG. NO, 100-902,
PROCLAIM® INSECTICIDE, EPA REG. NO, 100-904,
APPLICATION TO ADD POME FRUIT TO PROCLAIM®
INSECTICIDE LABEL**

Dear Mr. Harris,

Syngenta Crop Protection, Inc. is submitting, separately, a petition for the establishment of tolerances of emamectin benzoate in or on pome fruit (Crop Group 11). This submission is an application to amend the Proclaim Insecticide label to add directions for use on pome fruit. In Syngenta's recent letter to the EPA regarding the Agency's FY 2004 work plan, Syngenta listed this petition as one of its priorities. Syngenta also plans to submit, by June 1, 2003, a rationale supporting the classification of this proposed use as an organophosphate replacement.

In support of the tolerance petition for emamectin benzoate in or on pome fruit, Syngenta submitted residue studies for, the representative crop group commodities, apples and ears. Based on this proposed tolerance the Proclaim Insecticide label includes the following additional crops that are in the pome fruit group:

apple, crabapple, loquat, mayhaw, Oriental pear, pear and quince

Anticipating the EPA's upcoming approval of the use of Proclaim Insecticide on fruiting vegetables, leafy vegetables including Brassica, and turnip tops, we chose to submit the pending version of the Proclaim Insecticide label with the proposed additional use on pome fruit.

In addition to the accompanying petition for tolerance Syngenta is submitting the following:

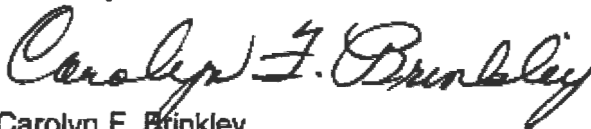
1. An application for amended registration of Proclaim Insecticide (EPA Form 8570-1)
2. Certification with Respect to Citation of Data Form
3. Data Matrix

4. Six copies of the proposed label – one copy with these revisions marked:
 - a. Added pome fruit directions for use
 - b. Deleted use restrictions from the General Information Section and created separate use restrictions for vegetables and pome fruit since some restrictions are not applicable to both crops
 - c. In the vegetable directions for use tables added the minimum application interval and the maximum amount allowed per application and per season.
 - d. Added a statement regarding chemigation to the container label.
 - e. Revised the date of the label to 3/26/03.

We recognize that the emamectin technical label must also be revised to include this additional use. We prefer to submit that label when the EPA is ready to set the pome fruit tolerance. If that is not acceptable, please let us know.

Thank you for your review of this application. If you have questions or comments, please contact me. I can be reached at (336) 632-2838 or via e-mail at carolyn.brinkley@sygenta.com.

Sincerely,



Carolyn F. Brinkley
Sr. Regulatory Product Manager
Regulatory Affairs

Enclosures: EPA Application for Amended Registration (8570-1)
Certification with Respect to Citation of Data
Six copies of proposed label – one with revisions marked



U.S. ENVIRONMENTAL PROTECTION AGENCY
Office of Pesticide Programs
Registration Division (7505C)
1200 Pennsylvania Ave., NW
Washington, D.C. 20460

EPA Reg. Number:

100-902

Date of

4/18/2003

NOTICE OF PESTICIDE:

☒ Registration

☐ Reregistration

(under FIFRA, as amended)

Term of Issuance:

Conditional, extended until
5/1/04

Name of Pesticide Product:

Emamectin Benzoate
Technical

Name and Address of Registrant (include ZIP Code):

Carolyn Brinkley
Syngenta Crop Protection, Inc.
PO Box 18300
Greensboro, NC 27419

Note: Changes in labeling differing in substance from that accepted in connection with this registration must be submitted to and accepted by the Registration Division prior to use of the label in commerce. In any correspondence on this product always refer to the above EPA registration number.

On the basis of information furnished by the registrant, the above named pesticide is hereby registered/reregistered under the Federal Insecticide, Fungicide and Rodenticide Act.

Registration is in no way to be construed as an endorsement or recommendation of this product by the Agency. In order to protect health and the environment, the Administrator, on his motion, may at any time suspend or cancel the registration of a pesticide in accordance with the Act. The acceptance of any name in connection with the registration of a product under this Act is not to be construed as giving the registrant a right to exclusive use of the name or to its use if it has been covered by others.

The above product was conditionally registered on 5/19/99 with an expiration date of 5/1/02. The registration was extended on 4/19/02 by EPA until 5/1/03. This letter serves to extend the conditional registration expiration date for this product an additional year, i.e. until 5/1/04.

This time extension will allow for review of an estuarine/marine invertebrate life-cycle study (guideline OPP 72-4b = OPPTS 850.1350) which was noted as a condition of registration for end use products EPA Registration # 100-903 and # 100-904. After the EPA denial of a Syngenta waiver request the registrant agreed to run the study. The study was submitted on 1/7/03, assigned MRID 458330-01, and is currently in review.

Signature of Approving Official:

Thomas C. Harris, Biologist
Insecticide-Rodenticide Branch
Registration Division (7504C)

Date:

4/18/03

Thomas Harris

01/02/2003 03:50 PM

To: carolyn.brinkley@syngenta.com, Charles
Stafford/DC/USEPA/US@EPA
cc: bill.helke@syngenta.com, Francis Griffith/DC/USEPA/US@EPA
Subject: Re: FW: Send in quantitative emamectin "degrade" stds in the year
2 003

MESSAGES BELOW FOR BOTH SYNGENTA AND EPA/ACL:

Carolyn (Syngenta),

The contact for analytical samples is:

Analytical Chemistry Branch

EPA/OPP/BEAD/ACB

Environmental Science Center

701 Mapes Road

Fort Mead, Maryland 20755-5350 [include full zip or it will not get there!]

attn: Charles Stafford

(410) 305-2914

When you send the samples you should also include the relevant MSDS and Certificate of Analysis.

I've cc'd the lab so they're aware of what you're working on.

-Tom

Chuck, Dick (EPA/ACL):

If you read the trail below you'll notice that Syngenta is wondering if they should submit what they have now and the rest later or wait until it's all done. If you have a preference please let me and Carolyn Brinkley (Syngenta) know. Thanks.

-Tom

Tom Harris

EPA/OPPTS/OPP/RD/IRB

(703) 308-9423

harris.thomas@epa.gov

carolyn.brinkley@syngenta.com



carolyn.brinkley@syngenta.com

01/02/2003 10:40 AM

To: Thomas Harris/DC/USEPA/US@EPA
cc: bill.helke@syngenta.com
Subject: FW: Send in quantitative emamectin "degrade" stds in the year 2
003

Hi Tom,

When John Hott was handling emamectin, EPA asked us to send them analytical standards for the ema metabolites. We sent what we had at the time and agreed to send the rest in 2003. We can provide some of the requested material now but not all of it. Are you the contact for this update?

> -----Original Message-----

> From: Helke Bill USGR

> Sent: Thursday, January 02, 2003 10:24 AM

> To: Brinkley Carolyn USGR

> Subject: RE: Send in quantitative emamectin "degrade" stds in the

> year 2003
>
> Hi Carolyn:
>
> Oh, lucky you! Emamectin is such a lovely compound to work with in the
> lab.
>
> According to phone conversation with John last year, EPA would take 250
> mg. of qualitative standards for their initial work, to be followed up
> with an additional 250 mg. of "analytical grade" standards once purified.
> We shipped the qualitative standards last year and promised to purify
> these as time permitted during 2002 and into 2003.
>
> Purification of these metabolites is not trivial and is only partially
> complete. To complicate things, our group size has been reduced by two
> Olsten temps in 2003 - one of those temps was the person I had working on
> this project. We will continue to work on purification of these but at
> reduced pace as time permits. Status of each is listed below:
>
> NOA 438376 = "8,9-ZMA": The most difficult one to purify.
Degrades
> as you work with it. Purification is two-step process. First step
> completed; Lengthy second step just started.
>
> NOA 438309 = "AB-1a/L'649": Purified, inventoried, ready to ship.
>
> NOA 415692 = "MFB1a/L'599": Purified, inventoried, ready to ship.
>
> NOA 415693 = "FAB1a/L'831": Purification is two-step process. First
> step completed, Lengthy second step partially completed.
>
> In light of the above and until I can get a better handle on our initial
> 2003 project workload (study starts/etc.), I won't promise anything in the
> way of delivery dates for the two that are not ready. Would you like us
> to ship the two that ARE ready to EPA in the interim, or would you prefer
> to wait and ship all four at the same time?
>
> Sincerely,
>
> Bill
> -----Original Message-----
> From: Brinkley Carolyn USGR
> Sent: Monday, December 23, 2002 1:29 PM
> To: Helke Bill USGR
> Subject: FW: Send in quantitative emamectin "degrade" stds in the
> year 2003
> Importance: High
>
> Bill, I am handling emamectin now - John is working with other ai's.
> According to the note from John Hott below, we owe the EPA additional
> emamectin in Jan '03. According to the attachments that John sent, we
> sent what we had at the time with the promise to send the remainder in
> '03. I am following up with you on this. Please get back to me.
>
> Thanks,
>
> -----Original Message-----
> From: Hott John USGR
> Sent: Monday, December 16, 2002 2:55 PM
> To: Brinkley Carolyn USGR

> Subject: RE: Send in quantitative emamectin "degradate" stds in the
> year 2003
>
> Carolyn,
>
> As part of the enforcement of the analytical methods for emamectin
> registrations, we were suppose to deposit enough standard material in the
> EPA depository. We did not have any (or very little of maybe questionable
> quality) to supply them with. Syngenta, via Greg Watson and his contact
> at the depository, agreed to supply them with quantitative stds in 2003
> (see the email below).
> John
> << Message: Emamectin Degradate Stds >> << Message: RE:
Emamectin
> Benzoate degradate samples need to go to Fort Mead >>



carolyn.brinkley@syngenta.com

11/19/2002 05:26 PM

To: Thomas Harris/DC/USEPA/US@EPA

cc: steve.r.miller@syngenta.com, merrill.tisdell@syngenta.com,
larry.zang@syngenta.com, leah.rosenheck@syngenta.com,
robert.wurz@syngenta.com, roy.boykin@syngenta.com

Subject: EPA ltr ema REI change mtg request 11-02

Via Electronic Mail

November 13, 2002

*- HED declined meeting
- REI set by CFR; any change
would be long process*

Mr. Thomas Harris

Insecticide-Rodenticide Branch

Office of Pesticide Programs (7504C)

U. S. Environmental Protection Agency

Ariel Rios Building

1200 Pennsylvania Avenue, N.W.

Washington, D.C. 20460

SUBJECT: EMAMECTIN BENZOATE

EPA REG. NO. 100-902

REQUEST FOR MEETING TO DISCUSS STUDY TO ADDRESS CHANGE
IN REI

Dear Mr. Harris:

Syngenta Crop Protection, Inc. is requesting a meeting to discuss a study that we believe will allow a reduction in the Restricted Entry Interval (REI) for emamectin benzoate-based products. The current REI is 48 hours based on the acute toxicity category 1 for emamectin benzoate technical. The trigger for this acute toxicity category based on the results of an eye irritation study in the rabbit. In 1999 Syngenta requested a reduction of this REI from 48 hours to 12 hours, however the Agency concluded that the reduction, based on the existing data and the information that Syngenta provided, was not justified. Following is a summary of the previous actions related to this request and an alternative testing proposal that Syngenta asks to discuss with the HED toxicologist(s) and risk assessors.

BACKGROUND

In 1998 and 1999 Syngenta (then Novartis) submitted proposals to the EPA to establish a 12-hour REI for the emamectin benzoate-based end-use insecticide product, Proclaim (EPA Reg. No. 100-904). [This reduction in REI, if acceptable to the EPA, would also have applied to the end-use insecticide, Denim (EPA Reg. No. 100-903) as well.] Syngenta's proposal was based on existing data. In a review dated May 10, 1999 the EPA stated that "the Agency considers the REI established under the requirements of CFR 156.208 [WPS] as an "interim" [interval] until a review of entry residue exposure data (with toxicity endpoints) is completed during the reregistration (or registration) process." However, the Agency went on to say that it has no mechanism for using skin and eye irritation categories to determine the appropriate REI, and currently only the dermal toxicity endpoint is used to assess risk with respect to postapplication exposures. EPA noted that until an appropriate mechanism is found for using skin and eye irritation potentials as an endpoint to assess possible risk with respect to postapplication exposures, the WPS interim REI remains in effect for those two triggers.

In June 1999 Syngenta submitted a second proposal to reduce the REI for emamectin-based products using a risk assessment based on existing data.

Syngenta's proposal to the EPA contained these conclusions:

- Using dislodgeable foliar residue (DFR) data, primary eye irritation data, and conservative assumptions, Novartis calculated a "Tier 1" assessment for ocular exposure and risk. The assessment demonstrated a large margin of safety even at 0 hours after application.
- Low contact and low exposure characterize reentry activities will occur in the field between 12 and 48 hours after application.

In a review dated January 16, 2002 the EPA concluded again that the reduction of the REI was not supported based on the existing data and the risk assessment that Syngenta provided. HED stated that use of a "benchmark" dose from an acute study with an end-use product to develop an MOE for postapplication ocular risk was not acceptable. In addition the EPA stated that post application low contact activities such as weeding, pruning, and moving irrigation pipes, are actually not low contact with respect to potential eye irritation.

However, Syngenta believes that there is a way to develop data such that a mechanism to use eye irritation potential as an endpoint can be used to assess possible risk with respect to postapplication exposures. To that end, Syngenta proposes to conduct a 870.2400 Guideline study using 5 mg and 1 mg of technical emamectin benzoate as the applied dose. Results of the study will allow establishment of a NOAEL and a potential dose response for eye irritation.

Using exposure data from agricultural worker re-entry studies conducted by the ARTF (Agricultural Reentry Task Force) combined with the residue data obtained from an emamectin dislodgeable foliar residue study (MRID 440079-03), Syngenta calculated an upper-bound estimate of the amount of residue that could be transferred from treated foliage to a worker's hands. To provide a conservative estimate of the potential ocular dose that could result from transfer of pesticide residue from the hand to the eye, Syngenta assumed that all of the emamectin benzoate residue on one hand was inserted into one eye. This resulted in a theoretical dose of 0.029 mg emamectin to the eye.

Syngenta anticipates that the proposed eye irritation study will show a direct relationship between the amount of emamectin administered and the severity of the resulting irritation. The results of the proposed eye irritation study should be an acute Toxicity Category of III or IV. Using the results of the proposed eye irritation study with the theoretical maximum dose to workers, Syngenta believes that the margin of exposure will be adequate to allow the EPA to reduce the the REI for emamectin-based products from 48 hours to 12 hours.

Because Syngenta is proposing a mechanism to use eye irritation potential as an endpoint to assess possible risk with respect to postapplication exposures, we request an opportunity to discuss this approach with the EPA toxicologist(s) and risk assessor(s) before commencing the proposed study.

Syngenta is available to meet on the following dates:

Dec 16, 17, or 18.

We prefer to meet at 8:30 am but can meet in the afternoon if necessary.

Thank you for arranging this meeting. Please call if you have any questions or comments.

I can be reached at (336) 632-2838.

Sincerely yours,

Carolyn F. Brinkley

Sr. Regulatory Product Manager

Regulatory Affairs

bcc:



header.htm



image001.gif

 Thomas Harris

11/05/2002 09:54 AM

To: carolyn.brinkley@syngenta.com
cc: robert.wurz@syngenta.com, steven.wall@syngenta.com
Subject: Re: Enamectin - Estuarine Study

Thanks for the info. Hopefully, this will give us enough time to review the study before the 5/1/03 deadline for the conditional registrations. I will put a reminder on my calendar for April to check on this (please do the same on your calendar). If necessary, I can extend the registration again until the review is done.

Tom Harris
EPA/OPPTS/OPP/RD/IRB
(703) 308-9423
harris.thomas@epa.gov
carolyn.brinkley@syngenta.com

 carolyn.brinkley@syngenta.com

11/05/2002 08:54 AM

To: Thomas Harris/DC/USEPA/US@EPA
cc: steven.wall@syngenta.com, robert.wurz@syngenta.com
Subject: Enamectin - Estuarine Study

Dear Tom,

The draft of this report will be complete in a couple of weeks, so our plan is to submit the study by the end of this year.

Carolyn F. Brinkley
Sr. Regulatory ProductManager/Insecticides
abamectin, cyromazine, diazinon, emamectin benzoate, fenoxycarb, pirimicarb, profenofos, pymetrozine

Syngenta Crop Protection, Inc.
P.O. Box 18300
Greensboro, NC 27419-8300
Phone: 336 632 2838 Fax: 336 292 6374
E-Mail: carolyn.brinkley@syngenta.com



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D C 20460

SEP 26 2002

Carolyn Brinkley
Syngenta Crop Protection, Inc.
PO Box 18300
Greensboro, NC 27419

OFFICE
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Subject: labels related to emamectin tolerance 7F4845
EPA Reg. # 100-902, 100-903, 100-904
corrections required

Dear Ms. Brinkley,

Over the past year we have been exchanging labels and comments on the above labels related to tolerance petition 7F4845 (cotton, fruiting vegetables, leafy vegetables, leafy Brassica vegetables, tobacco). Submissions have been made via both traditional paper submissions as well as electronically via email. While the tolerance analysis is still under review, the labels require some corrections. Please make the following corrections and submit revised labels.

| Product, version | Action required |
|---|--|
| 100-902 emamectin technical paper submission 11/8/01 | CHANGE site list to 1) merge leafy Brassica greens and head and stem Brassica subgroups since the proposed tolerance is for the entire leafy Brassica group; 2) add turnip greens (leaves) as a separate crop; 3) move cotton to the main food crop list (tobacco is the only terrestrial non-food crop on the label). Note that this list goes under the directions for use not on front panel. |
| 100-903 Denim electronic submission 5/23/02 | In PPE under Precautionary Statements, CHANGE "long-sleeved shirt and long pants" to "coveralls worn over short-sleeved shirt and short pants" as on current accepted label or provide justification for change. Regardless of text, please send a paper submission for this label. |

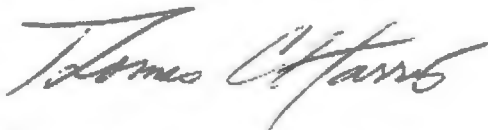
| Product, version | Action required |
|---|---|
| 100-904 Proclaim paper & electronic submission 7/24/02 | In the Directions for Use, Leafy Brassica vegetables, footnote regarding turnip greens: DELETE the text regarding dual purpose cultivars and only allow the use of "distinct cultivars ... edible leaves" It was decided that the prohibition against using the roots of the dual purpose varieties would be unenforceable. Retain the "do not use turnip roots for human food or animal feed" text in the footnote. |

For each product, submit five (5) paper copies of the label, an EPA Form 8570-1, and a cover letter (referencing this letter).

(Optional) It would also be helpful if you could submit a CD-ROM with an electronic copy of each proposed label in .PDF format (current draft instructions enclosed). All three electronic labels can be submitted on the same CD-ROM. Include a signed Certification with Respect to Label Integrity (enclosed) for each product, as well.

If you have any questions please contact me at (703) 308-9423 or Harris.Thomas@EPA.gov.

Sincerely yours,



Thomas C. Harris
Insecticide / Rodenticide Branch
Registration Division (7505C)
Office of Pesticide Programs

enclosures



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

SEP 24 2002

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Carolyn Brinkley
Syngenta Crop Protection, Inc.
PO Box 18300
Greensboro, NC 27419

Subject: Eamectin Technical, EPA Reg. # 100-902
label amendment submitted 11/8/01
accepted with comments

Dear Ms. Brinkley,

The revised labeling reference to above, submitted in connection with the registration under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended, is acceptable provided you incorporate the changes required by the Agency as listed below.

| Topic | Action required |
|---------------------------------|---|
| Directions for Use site list | DELETE existing single sentence paragraph listing sites: "This product may be used ... and head lettuce." |
| Front Panel site list | MOVE new site text (inserted between product name and active ingredient statement) from front panel to Directions for Use following "It is a violation of Federal law" The new site text replaces the old single sentence site paragraph deleted as per above. New site list has three items in a list format: "This product may be used only 1. Agricultural Crops 2. Use for which the U.S. EPA has accepted the required data 3. Use for experimental purposes" |

Submit two (2) copies of your final printed labeling incorporating the above changes prior to releasing your product for shipment. If the above provisions are not complied with the registration will be subject to cancellation in accordance with FIFRA Section 6(e). Your release for shipment of the product bearing the amended labeling constitutes acceptance of these conditions.

A copy of your label stamped "accepted with comments" is enclosed for your records.

If you have any questions please contact me at (703) 308-9423 or Harris.Thomas@EPA.gov.

Sincerely yours,

Thomas C. Harris
Insecticide / Rodenticide Branch
Registration Division (7505C)
Office of Pesticide Programs

enclosure

Emamectin Benzoate Technical

This product may be used only for formulation into an insecticide for the uses listed below (text in parenthesis refers to the general use pattern as referenced in 40CFR158):

1. Agricultural crops (Terrestrial Food Crop)

Head Lettuce and Celery; head and stem Brassica Vegetables [Broccoli, Brussels sprouts, Cabbage, Cauliflower, Cavolo broccolo, Chinese broccoli, Chinese (napa) cabbage, Chinese mustard cabbage, Kohlrabi].

2. Uses for which the U.S. EPA has accepted the required data and/or citations of data that the formulator has submitted in support of registration excluding any use strictly prohibited by this label.

3. Uses for experimental purposes that are in compliance with U.S. EPA requirements.

Active Ingredient:

Emamectin Benzoate (CAS No. 155569-91-8) _____ 97.0%

Other Ingredients: _____ 3.0%

Total: _____ 100.0%

KEEP OUT OF REACH OF CHILDREN

SKULL & CROSSBONES]

**DANGER/PELIGRO
POISON
[red type]**

[SKULL & CROSSBONES]

Si usted no entiende la etiqueta, busque a alguien para que se la explique a usted en detalle. (If you do not understand the label find someone to explain it to you in detail.)

See additional precautionary statements on label.

EPA Reg. No. 100-902
EPA Est. 41448-SW-1

Product of Switzerland

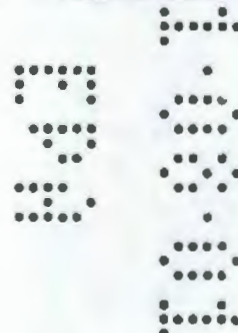
SCP 902A-L1(Draft-A)

Lot# _____
Net Weight: _____
Physical _____ kg
Assay _____ kg
Drum No. _____

**ACCEPTED
with COMMENTS
In EPA Letter Dated:
SEP 24 2002**

**Under the Federal Insecticide,
Fungicide, and Rodenticide Act,
as amended, for the pesticide
registered under EPA Reg. No.**

100-902



| FIRST AID | |
|---|--|
| If in eyes | <ul style="list-style-type: none"> • Hold eye open and rinse slowly and gently with water for 15-20 minutes. • Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. • Call a poison control center or doctor for treatment advice. |
| If on skin or clothing | <ul style="list-style-type: none"> • Take off contaminated clothing. • Rinse skin immediately with plenty of water for 15-20 minutes • Call a poison control center or doctor for treatment advice. |
| If inhaled | <ul style="list-style-type: none"> • Move person to fresh air. • If person is not breathing, call 911 or an ambulance, and then give artificial respiration, preferably mouth-to-mouth, if possible. • Call a poison control center or doctor for treatment advice. |
| If swallowed | <ul style="list-style-type: none"> • Call a poison control center or doctor immediately for treatment advice. • Have person sip glass of water if able to swallow. • Do not induce vomiting unless told to do so by a poison control center or doctor. • Do not give anything by mouth to an unconscious person. |
| NOTE TO PHYSICIAN | |
| <p>Recommendations for Medical Treatment for Emamectin Benzoate Acute Toxicity: Early signs of intoxication include mydriasis (dilated pupils), ataxia (unsteadiness), and muscle tremors. Toxicity following accidental ingestion of the concentrate can be minimized by inducing vomiting within ½ hour of exposure. If toxicity from exposure has progressed to cause severe vomiting, the extent of resultant fluid and electrolyte imbalance should be gauged. Appropriate supportive parenteral fluid replacement therapy should be given, along with other required supportive measures (such as maintenance of blood pressure levels) as indicated by clinical signs, symptoms, and measurements. In severe cases, observations should continue for at least several days until clinical condition is stable and normal. Since emamectin benzoate is believed to enhance GABA activity in animals, it is probably wise to avoid drugs that enhance GABA activity (barbiturates, benzodiazepines, valproic acid) in patients with potentially toxic emamectin benzoate exposure.</p> | |
| <p>Have the product container or label with you when calling a poison control center or doctor or going for treatment.</p> | |
| HOT LINE NUMBER | |
| <p>For 24 Hour Medical Emergency Assistance (Human or Animal) or Chemical Emergency Assistance (Spill, Leak, Fire, or Accident), Call 1-800-888-8372</p> | |

PRECAUTIONARY STATEMENTS

Hazards to Humans and Domestic Animals

Corrosive. Causes irreversible eye damage. Do not get in eyes or on clothing. Wear protective eyewear (goggles, face shield, or safety glasses) May be fatal if swallowed. Wash thoroughly with soap and water after handling and before eating, drinking, or using tobacco. Remove and wash contaminated clothing before reuse.

Environmental Hazards

This pesticide is toxic to fish, birds, mammals, and aquatic invertebrates. Do not discharge effluent containing this active ingredient into lakes, streams, ponds, estuaries, oceans, or other public waters, unless in accordance with the requirements of a National Pollutant Discharge Elimination System (NPDES) permit, and the permitting authority has been notified in writing prior to discharge. Do not discharge effluent containing this product into sewer systems without previously notifying the local sewage treatment plant authority. For guidance, contact your State Water Board or Regional Office of the EPA.

CONDITIONS OF SALE AND LIMITATION OF WARRANTY AND LIABILITY

NOTICE: Read the entire Directions for Use and Conditions of Sale and Limitation of Warranty and Liability before buying or using this product. If the terms are not acceptable, return the product at once, unopened, and the purchase price will be refunded.

The Directions for Use of this product should be followed carefully. It is impossible to eliminate all risks inherently associated with the use of this product. Crop injury, ineffectiveness or other unintended consequences may result because of such factors as manner of use or application, weather or crop conditions, presence of other materials or other influencing factors in the use of the product, which are beyond the control of SYNGENTA CROP PROTECTION, Inc. or Seller. All such risks shall be assumed by Buyer and User, and Buyer and User agree to hold SYNGENTA and Seller harmless for any claims relating to such factors.

SYNGENTA warrants that this product conforms to the chemical description on the label and is reasonably fit for the purposes stated in the Directions for Use, subject to the inherent risks referred to above, when used in accordance with directions under normal use conditions. This warranty does not extend to the use of the product contrary to label instructions, or under abnormal conditions or under conditions not reasonably foreseeable to or beyond the control of Seller or SYNGENTA, and Buyer and User assume the risk of any such use. SYNGENTA MAKES NO WARRANTIES OF MERCHANTABILITY OR OF FITNESS FOR A PARTICULAR PURPOSE NOR ANY OTHER EXPRESS OR IMPLIED WARRANTY EXCEPT AS STATED ABOVE.

In no event shall SYNGENTA or Seller be liable for any incidental, consequential or special damages resulting from the use or handling of this product. **THE EXCLUSIVE REMEDY OF THE USER OR BUYER, AND THE EXCLUSIVE LIABILITY OF SYNGENTA AND SELLER FOR ANY AND ALL CLAIMS, LOSSES, INJURIES OR DAMAGES (INCLUDING CLAIMS BASED ON BREACH OF WARRANTY, CONTRACT, NEGLIGENCE, TORT, STRICT LIABILITY OR OTHERWISE) RESULTING FROM THE USE OR HANDLING OF THIS PRODUCT, SHALL BE THE RETURN OF THE PURCHASE PRICE OF THE PRODUCT OR, AT THE ELECTION OF SYNGENTA OR SELLER, THE REPLACEMENT OF THE PRODUCT.**

SYNGENTA and Seller offer this product, and Buyer and User accept it, subject to the foregoing Conditions of Sale and Limitations of Warranty and of Liability, which may not be modified except by written agreement signed by a duly authorized representative of SYNGENTA.

DIRECTIONS FOR USE

It is a violation of Federal law to use this product in a manner inconsistent with its labeling.

This product may be used only to manufacture/formulate other insecticide products registered and labeled for use on head and stem Brassica vegetables, celery, and head lettuce.

STORAGE AND DISPOSAL

Do not store near food or feed. Do not contaminate water, food, or feed by storage or disposal.

Store in a tightly closed original container in a cool, dry place.

Pesticide Disposal

Pesticide wastes are acutely hazardous. Improper disposal of excess pesticide, or rinsate is a violation of Federal law. If these wastes cannot be disposed of by use according to label instructions, contact your State Pesticide or Environmental Control Agency, or the Hazardous Waste representative at the nearest EPA Regional Office for guidance. Pesticide that cannot be used or chemically reprocessed must be disposed of according to federal, state, or local procedures under the Resource Conservation and Recovery Act.

Container Disposal

Bulk

Thoroughly clean container before reuse. Consult federal, state, or local disposal authorities for approved alternative procedures.

250 Gal Mini Bulk

This is a refillable container that must be returned to an authorized Syngenta refilling facility for refilling or disposal.

Other Containers

Triple rinse (or equivalent). Then offer for recycling or reconditioning, or puncture and dispose of in a sanitary landfill, or by other procedures approved by state and local authorities.

Note: For minor spills, leaks, etc. follow all precautions indicated on this label and clean up immediately. Take special care to avoid contamination of equipment and facilities during cleanup procedures and disposal of wastes.

©2001 Syngenta

For non-emergency (e.g. current product information)
call Syngenta Crop Protection, Inc. at 1-800-334-9481

Syngenta Crop Protection, Inc.
Greensboro, North Carolina 27409
www.syngenta-us.com

SCP 902A-L1(Draft-A)

Z:LABEL-WE/EMATECH902A-L1(DRAFT-A) – ccg – 11/5/01

August 30, 2001 –draft
revised label to EPA,
revised first aid statements
according to PR Notice
2001-1, revised ingredient
statement according to new
CSF and prod. chem,
revised and added storage
and disposal statements,
specified on front panel end-
use product uses supported
for this active ingredient.
Corrected label by adding
Spanish signal word and
warning statement, deleted
chemical name of active –
common name and CAS no.
are sufficient, changed all
references to Novartis to
Syngenta and replaced
Warranty statement with
new Syngenta Warranty
Statement, changed country
of origin to Switzerland,
revised ingredient statement
per PR Notices 97-5 & 97-6
Nov. 5, 2001 – draft –
revised current uses

Z:LABELLE-W/EMATECH902A-L1(DRAFT-A) – ccg – 11/5/01



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

11/15/2001

JOHN L. HOTT
SYNGENTA CROP PROTECTION, INC.
P.O. BOX 18300
GREENSBORO NC 274198300

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

PRODUCT NAME: EMAMECTIN TECHNICAL
COMPANY NAME: SYNGENTA CROP PROTECTION, INC.
OPP IDENTIFICATION NUMBER: 286151
EPA REGISTRATION NUMBER: 100-902
EPA RECEIPT DATE: 11/08/2001

SUBJECT: RECEIPT OF AMENDMENT

DEAR REGISTRANT:

The Office of Pesticide Programs has received your application for an amendment and it has passed an administrative screen for completeness.

During the initial screen we determined that the application qualifies for fast track review. The package will now be forwarded to the Product Manager for review to determine its acceptability.

If you have any questions, please contact Insecticide Branch, Product Manager 03, at (703) 305-6891.

Sincerely,

J. Wrice

Front End Processing Staff
Information Services Branch
Program Management and Support Division

A

B

Syngenta Crop Protection, Inc. Tel 336 637 6000
P.O. Box 18300
Greensboro, NC 27419-8300



Hand Delivered

November 8, 2001

Office of Pesticide Programs (H7504C)
U.S. Environmental Protection Agency
Ariel Rios Building
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Attn: Mr. Thomas Harris, PM IRB

SUBJECT: EMAMECTIN TECHNICAL
EPA REG. NO. 100-902
AMENDED TECHNICAL LABELS

Dear Mr. Harris:

Per your request, I am enclosing copies of Emamectin Technical labels with the addition of detailed "use sites." One version of the label has listed the current use sites. The other version submitted has the current use sites, plus the current pending use sites. Enclosed are five copies (with one copy highlighted to indicate the location of the change) of the each revised label.

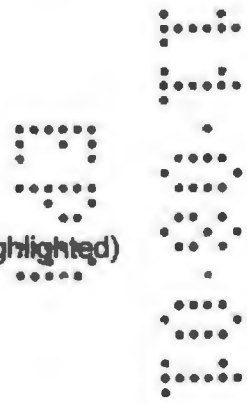
To complete this action, an EPA Form 8570-1 is included.

Thank you for handling this matter. If you have any questions or require additional information, please call me at (336) 632-7096.

Sincerely,

John L. Hott, Ph.D.
Regulatory Product Manager
Regulatory Affairs

Enclosures: Two versions of revised labeling (5 copies each, one highlighted)
EPA Form 8570-1





United States
Environmental Protection Agency
Washington, DC 20460

☐ Registration
☒ Amendment
☐ Other

OPP Identifier Number

~~283759~~
286151

Application for Pesticide - Section I

| | | |
|---|--------------------------------------|--|
| 1. Company/Product Number 100-902 | 2. EPA Product Manager Tom Harris | 3. Proposed Classification <input checked="" type="checkbox"/> None <input type="checkbox"/> Restricted |
| 4. Company/Product (Name) Emamectin Technical | PM# IRB | |
| 5. Name and Address of Applicant (Include ZIP Code) Syngenta Crop Protection, Inc. P. O. Box 18300 Greensboro, NC 27419 <input type="checkbox"/> Check if this is a new address | | 6. Expedited Review. In accordance with FIFRA Section 3(c)(3) (b)(i), my product is similar or identical in composition and labeling to: EPA Reg. No. _____ Product Name _____ |

Section - II

| | |
|--|--|
| <input checked="" type="checkbox"/> Amendment - Explain below. | <input type="checkbox"/> Final printed labels in response to Agency letter dated _____ |
| <input type="checkbox"/> Resubmission in response to Agency letter dated _____ | <input type="checkbox"/> "Me Too" Application. |
| <input type="checkbox"/> Notification - Explain below. | <input type="checkbox"/> Other - Explain below. |

Explanation: Use additional page(s) if necessary. (For Section I and Section II.).
Adding detailed use sites, per communication with Tom Harris.

Section - III

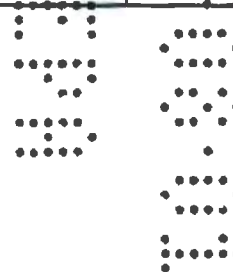
| | | | |
|--|--|--|---|
| 1. Material This Product Will Be Packaged In: | | 2. Type of Container | |
| Child-Resistant Packaging <input type="checkbox"/> Yes* <input checked="" type="checkbox"/> No | Unit Packaging <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No | Water Soluble Packaging <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No | <input checked="" type="checkbox"/> Metal <input type="checkbox"/> Plastic <input type="checkbox"/> Glass <input type="checkbox"/> Paper <input type="checkbox"/> Other (Specify) _____ |
| *Certification must be submitted | | | |
| If "Yes" Unit Packaging wgt. | No. per Container | If "Yes" Unit Packaging wgt. | No. per container |
| 3. Location of Net Contents Information <input type="checkbox"/> Label <input checked="" type="checkbox"/> Container | | 4. Size(s) Retail Container 2 to 5 pounds | |
| 5. Location of Label Directions <input checked="" type="checkbox"/> On Label <input type="checkbox"/> On Labeling accompanying product | | 6. Manner in Which Label is Affixed to Product <input type="checkbox"/> Lithograph <input checked="" type="checkbox"/> Paper glued <input type="checkbox"/> Stenciled <input type="checkbox"/> Other _____ | |

Section - IV

| | | | |
|--|--|--|--|
| 1. Contact Point (Complete items directly below for identification of individual to be contacted, if necessary, to process this application.) | | | |
| Name John L. Hott | | Title Regulatory Product Manager | |
| Telephone No (Include Area Code) 336-632-7096 | | | |
| Certification I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law. | | | 6. Date Application Received (Stamped) |
| 2. Signature | | 3. Title Regulatory Product Manager | |
| 4. Typed Name John L. Hott | | 5. Date November 8, 2001 | |

EPA Form 8570-1 (Rev. 8-94) Previous editions are obsolete.

100-902
300 only





United States
Environmental Protection Agency
Washington, DC 20480

☐ Registration
☐ Amendment
☐ Other

OPP Identifier Number

286151

Application for Pesticide - Section I

| | | |
|---|------------------------|--|
| 1. Company/Product Number | 2. EPA Product Manager | 3. Proposed Classification <input type="checkbox"/> None <input type="checkbox"/> Restricted |
| 4. Company/Product (Name) | PM# | |
| 5. Name and Address of Applicant (Include ZIP Code) | | 6. Expedited Review. In accordance with FIFRA Section 3(c)(3) (b)(i), my product is similar or identical in composition and labeling to: EPA Reg. No. _____ Product Name _____ |
| <input type="checkbox"/> Check if this is a new address | | |

Section - II

| | |
|--|--|
| <input type="checkbox"/> Amendment - Explain below. | <input type="checkbox"/> Final printed labels in response to Agency letter dated _____ |
| <input type="checkbox"/> Resubmission in response to Agency letter dated _____ | <input type="checkbox"/> "Me Too" Application. |
| <input type="checkbox"/> Notification - Explain below. | <input type="checkbox"/> Other - Explain below. |

Explanation: Use additional page(s) if necessary. (For section I and Section II.)

Section - III

| | | | | | |
|---|---|--|--|---|--|
| 1. Material This Product Will Be Packaged In: | | | | 2. Type of Container | |
| Child-Resistant Packaging <input type="checkbox"/> Yes* <input type="checkbox"/> No | Unit Packaging <input type="checkbox"/> Yes <input type="checkbox"/> No | Water Soluble Packaging <input type="checkbox"/> Yes <input type="checkbox"/> No | | <input type="checkbox"/> Metal | |
| | | | | <input type="checkbox"/> Plastic | |
| | | | | <input type="checkbox"/> Glass | |
| | | | | <input type="checkbox"/> Paper | |
| | | | | <input type="checkbox"/> Other (Specify) _____ | |
| 3. Location of Net Contents Information <input type="checkbox"/> Label <input type="checkbox"/> Container | | 4. Size(s) Retail Container | | 5. Location of Label Directions <input type="checkbox"/> On Label <input type="checkbox"/> On Labeling accompanying product | |
| 6. Manner in Which Label is Affixed to Product <input type="checkbox"/> Lithograph <input type="checkbox"/> Paper glued <input type="checkbox"/> Stenciled | | <input type="checkbox"/> Other _____ | | | |

Section - IV

| | | | |
|--|--|-----------------------------------|---|
| 1. Contact Point (Complete items directly below for identification of individual to be contacted, if necessary, to process this application.) | | | |
| Name | | Title | |
| | | Telephone No. (Include Area Code) | |
| Certification I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law. | | | 8. Date Application Received (Stamped) |
| 2. Signature | | 3. Title | |
| 4. Typed Name | | 5. Date | |

PAPERWORK REDUCTION ACT NOTICE and INSTRUCTIONS

PAPERWORK REDUCTION ACT NOTICE: Public reporting burden for this collection of information is estimated to average 0.85 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding the burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Chief, Information Policy Branch, (2136), U.S. Environmental Protection Agency, 401 M Street, SW, Washington, DC 20460.

INSTRUCTIONS: This form is to be used for all applications for new registration, end use reregistration, amendment, resubmission, to applications for notifications, final printed labeling, reregistration, etc. In order to process an application for a new registration submitted on this form, the following material must accompany the application:

1. Certification with Respect to Citation of Data (EPA Form 8570-29). [If not exempted by 40 CFR 152.81 (b) (4)];
2. Confidential Statement of Formula (EPA Form 8570-4);
3. Formulator's Exemption Statement (EPA Form 8570-27);
4. Five copies of draft labeling;
5. Three copies of any data submitted;
6. Authorization letter where applicable;
7. Matrices where applicable.

Submission of Labeling - Labeling should first be submitted in the form of draft labels with all applications for new registration. Such draft labels may be in the form of typed label text on 8.5 x 11 inch paper for submission or a mockup of the proposed label. If prepared for mockup, it should be constructed in a way as to facilitate storage in an 8.5 x 11 inch file. Mockup labels significantly smaller than 8.5 x 11 inches should be mounted on 8.5 x 11 inch paper for submission.

Submission of Data - Data submitted in support of this application must be submitted in accordance with PR Notice 86-5.

SPECIFIC INSTRUCTIONS: Please read the instructions listed below before completing this application. First determine the type of registration action, listed in Block A, for which you are submitting this application. For applications submitted in connection with New Registration actions, Sections I, III, and IV must be completed by the applicant. For applications submitted in connection with amended reregistration actions, resubmissions, notifications, reregistrations, etc., Sections I, II, and IV must be completed by the applicant.

Block A - Check the appropriate action for which you are submitting this form.

SECTION I - This section must be completed, as applicable, for all registration actions.

1. **Company/Product Number** - Insert your Company Number, if one has been assigned by EPA. This number may have been assigned to you as a basic registrant, a distributor, or as an establishment. If your product is registered, insert the Product Number.
2. **EPA Product Manager** - If known, fill in the name and PM number of the EPA Product Manager.
3. **Proposed Classification** - Specify the proposed classification of this product.
4. **Product Name** - Enter the complete product name of this pesticide as it will appear on the label. The name must be specific to this product only. Duplication of names is not permitted among products of the same company. Do not include any brand name or company line designations.
5. **Name and Address of Applicant** - The name of the firm or person and address shown in your application is the person or firm to whom the registration will be issued. If you are acting in behalf of another party, you must submit authorization from that party to act for them in registration matters. An applicant not residing in the United States must have an authorized agent residing in the United States to act for them in all registration matters. The name and complete mailing address of such an agent must accompany this application.
6. **Expedited Review** - FIFRA section 3 (e) 3 (B) provides for expedited review of applications for registration, or amendments to existing registrations, that are similar or identical to other pesticide products that are currently registered with the EPA. In order for your application to be eligible for expedited review, you must provide us with the EPA Registration Number and product name of the product you believe is similar to or identical to your product. The product must be similar or identical in both formulation and labeled uses.

SECTION II - This section must be completed for all applications submitted to amend the registration only of a currently registered product (Amendment), for a resubmission in response to an Agency letter, for notifications to the Agency, for the submission of final printed labeling, for reregistration and for any other action that pertains to a specific EPA-registered product. This section is not to be used for a new application for registration.

1. **Subject of submission** - Check the applicable block and provide the Agency letter date if appropriate. Provide a brief explanation of the purpose(s) for the submission, such as "the addition of a site, pest or crop (specify)"; "amend the Confidential Statement of Formula by..."; "reregistration submission"; "general label revision of use directions." Attach a separate page if additional space is needed.

SECTION III (Packaging and Container Information) - This Section must be completed for all applications submitted in connection with new registration or applicable amendments.

1. **Type of Packaging** - Check the appropriate block if your product will be packaged in the indicated packaging types. Indicate the size of the individual packets and number per retail container.
2. **Type of Retail Container** - Indicate type of container in which product will be marketed.
3. **Location of Net Contents** - Indicate the location of the net contents information for your product.
4. **Size(s) of Retail Container** - Specify the net contents of all retail containers for your product.
5. **Location of Use Directions** - Indicate the location of the use directions for your product.
6. **Manner in which label is affixed to product** - Indicate the method product label is attached to retail container.

SECTION IV (Contact Point) - This Section must be completed for all applications for Registration actions, i.e., new products registration, resubmission, "me-too," reregistration, etc.

- 1-5. Self-explanatory.
6. EPA Use Only.



United States
Environmental Protection Agency
Washington, DC 20460

☐ Registration
☐ Amendment
☐ Other

OPP Identifier Number

286151

Application for Pesticide - Section I

| | | |
|--|---|---|
| 1. Company/Product Number | 2. EPA Product Manager | 3. Proposed Classification <input type="checkbox"/> None <input type="checkbox"/> Restricted |
| 4. Company/Product (Name) | PM# | |
| 5. Name and Address of Applicant (Include ZIP Code) <input type="checkbox"/> Check if this is a new address | 5. Expedited Review. In accordance with FIFRA Section 3(c)(3) (b)(ii), my product is similar or identical in composition and labeling to: EPA Reg. No. _____ Product Name _____ | |

Section - II

| | |
|--|--|
| <input type="checkbox"/> Amendment - Explain below. | <input type="checkbox"/> Final printed labels in response to Agency letter dated _____ |
| <input type="checkbox"/> Resubmission in response to Agency letter dated _____ | <input type="checkbox"/> "Me Too" Application. |
| <input type="checkbox"/> Notification - Explain below. | <input type="checkbox"/> Other - Explain below. |

Explanation: Use additional page(s) if necessary. (For section I and Section II.)

Section - III

| | | | | | |
|---|---|--|--|----------------------|--|
| 1. Material This Product Will Be Packaged In: | | | | 2. Type of Container | |
| Child-Resistant Packaging <input type="checkbox"/> Yes <input type="checkbox"/> No | Unit Packaging <input type="checkbox"/> Yes <input type="checkbox"/> No | Water Soluble Packaging <input type="checkbox"/> Yes <input type="checkbox"/> No | <input type="checkbox"/> Metal <input type="checkbox"/> Plastic <input type="checkbox"/> Glass <input type="checkbox"/> Paper <input type="checkbox"/> Other (Specify) _____ | | |
| Certification must be submitted If "Yes" Unit Packaging wgt. No. per container If "Yes" Package wgt. No. per container | | | | | |
| 3. Location of Net Contents Information <input type="checkbox"/> Label <input type="checkbox"/> Container | | 4. Size(s) Retail Container | 5. Location of Label Directions <input type="checkbox"/> On Label <input type="checkbox"/> On Labeling accompanying product | | |
| 6. Manner in Which Label is Affixed to Product <input type="checkbox"/> Lithograph <input type="checkbox"/> Paper glued <input type="checkbox"/> Stenciled | | <input type="checkbox"/> Other _____ | | | |

Section - IV

| | | | | | |
|---|--|----------|--|-----------------------------------|--|
| 1. Contact Point (Complete items directly below for identification of individual to be contacted, if necessary, to process this application.) | | | | | |
| Name | | Title | | Telephone No. (Include Area Code) | |
| Certification I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law. | | | | | 6. Date Application Received (Stamped) |
| 2. Signature | | 3. Title | | | |
| 4. Typed Name | | 5. Date | | | |

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5. **Name and Address of Applicant** - The name of the firm or person and address shown in your application is the person or firm to whom the registration will be issued. If you are acting in behalf of another party, you must submit authorization from that party to act for them in registration matters. An applicant not residing in the United States must have an authorized agent residing in the United States to act for them in all registration matters. The name and complete mailing address of such an agent must accompany this application.
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2. **Type of Retail Container** - Indicate type of container in which product will be marketed.
3. **Location of Net Contents** - Indicate the location of the net contents information for your product.
4. **Size(s) of Retail Container** - Specify the net contents of all retail containers for your product.
5. **Location of Use Directions** - Indicate the location of the use directions for your product.
6. **Manner in which label is affixed to product** - Indicate the method product label is attached to retail container.

SECTION IV (Contact Point) - This Section must be completed for all applications for Registration actions, i.e., new products registration, resubmission, "me-too," reregistration, etc.

- 1-5. Self-explanatory.
6. EPA Use Only.

Eamectin Benzoate Technical

Revised current use sites

This product may be used only for formulation into an insecticide for the uses listed below (text in parenthesis refers to the general use pattern as referenced in 40CFR158):

1. Agricultural crops (Terrestrial Food Crop)

Head Lettuce and Celery; head and stem Brassica Vegetables [Broccoli, Brussels sprouts, Cabbage, Cauliflower, Cavolo broccolo, Chinese broccoli, Chinese (napa) cabbage, Chinese mustard cabbage, Kohlrabi].

2. Uses for which the U.S. EPA has accepted the required data and/or citations of data that the formulator has submitted in support of registration excluding any use strictly prohibited by this label.

3. Uses for experimental purposes that are in compliance with U.S. EPA requirements.

Active Ingredient:

Eamectin Benzoate (CAS No. 155569-91-8) 97.0%

Other Ingredients: 3.0%

Total: 100.0%

KEEP OUT OF REACH OF CHILDREN

SKULL & CROSSBONES]

DANGER/PELIGRO
POISON
[red type]

[SKULL & CROSSBONES]

Si usted no entiende la etiqueta, busque a alguien para que se la explique a usted en detalle. (If you do not understand the label find someone to explain it to you in detail.)

See additional precautionary statements on label.

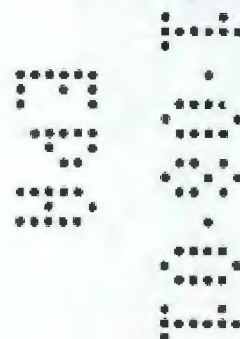
EPA Reg. No. 100-902

EPA Est. 41448-SW-1

Product of Switzerland

SCP 902A-L1(Draft-A)

Lot# _____
Net Weight: _____
Physical _____ kg
Assay _____ kg
Drum No. _____



| FIRST AID | |
|--|--|
| If in eyes | <ul style="list-style-type: none"> • Hold eye open and rinse slowly and gently with water for 15-20 minutes. • Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. • Call a poison control center or doctor for treatment advice. |
| If on skin or clothing | <ul style="list-style-type: none"> • Take off contaminated clothing. • Rinse skin immediately with plenty of water for 15-20 minutes • Call a poison control center or doctor for treatment advice. |
| If inhaled | <ul style="list-style-type: none"> • Move person to fresh air. • If person is not breathing, call 911 or an ambulance, and then give artificial respiration, preferably mouth-to-mouth, if possible. • Call a poison control center or doctor for treatment advice. |
| If swallowed | <ul style="list-style-type: none"> • Call a poison control center or doctor immediately for treatment advice. • Have person sip glass of water if able to swallow. • Do not induce vomiting unless told to do so by a poison control center or doctor. • Do not give anything by mouth to an unconscious person. |
| NOTE TO PHYSICIAN | |
| <p>Recommendations for Medical Treatment for Emamectin Benzoate Acute Toxicity: Early signs of intoxication include mydriasis (dilated pupils), ataxia (unsteadiness), and muscle tremors. Toxicity following accidental ingestion of the concentrate can be minimized by inducing vomiting within ½ hour of exposure. If toxicity from exposure has progressed to cause severe vomiting, the extent of resultant fluid and electrolyte imbalance should be gauged. Appropriate supportive parenteral fluid replacement therapy should be given, along with other required supportive measures (such as maintenance of blood pressure levels) as indicated by clinical signs, symptoms, and measurements. In severe cases, observations should continue for at least several days until clinical condition is stable and normal. Since emamectin benzoate is believed to enhance GABA activity in animals, it is probably wise to avoid drugs that enhance GABA activity (barbiturates, benzodiazepines, valproic acid) in patients with potentially toxic emamectin benzoate exposure.</p> | |
| Have the product container or label with you when calling a poison control center or doctor or going for treatment. | |
| HOT LINE NUMBER | |
| <p>For 24 Hour Medical Emergency Assistance (Human or Animal) or Chemical Emergency Assistance (Spill, Leak, Fire, or Accident), Call 1-800-888-8372</p> | |

PRECAUTIONARY STATEMENTS

Hazards to Humans and Domestic Animals

Corrosive. Causes irreversible eye damage. Do not get in eyes or on clothing. Wear protective eyewear (goggles, face shield, or safety glasses) May be fatal if swallowed. Wash thoroughly with soap and water after handling and before eating, drinking, or using tobacco. Remove and wash contaminated clothing before reuse.

Environmental Hazards

This pesticide is toxic to fish, birds, mammals, and aquatic invertebrates. Do not discharge effluent containing this active ingredient into lakes, streams, ponds, estuaries, oceans, or other public waters, unless in accordance with the requirements of a National Pollutant Discharge Elimination System (NPDES) permit, and the permitting authority has been notified in writing prior to discharge. Do not discharge effluent containing this product into sewer systems without previously notifying the local sewage treatment plant authority. For guidance, contact your State Water Board or Regional Office of the EPA.

CONDITIONS OF SALE AND LIMITATION OF WARRANTY AND LIABILITY

NOTICE: Read the entire Directions for Use and Conditions of Sale and Limitation of Warranty and Liability before buying or using this product. If the terms are not acceptable, return the product at once, unopened, and the purchase price will be refunded.

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SYNGENTA warrants that this product conforms to the chemical description on the label and is reasonably fit for the purposes stated in the Directions for Use, subject to the inherent risks referred to above, when used in accordance with directions under normal use conditions. This warranty does not extend to the use of the product contrary to label instructions, or under abnormal conditions or under conditions not reasonably foreseeable to or beyond the control of Seller or SYNGENTA, and Buyer and User assume the risk of any such use. SYNGENTA MAKES NO WARRANTIES OF MERCHANTABILITY OR OF FITNESS FOR A PARTICULAR PURPOSE NOR ANY OTHER EXPRESS OR IMPLIED WARRANTY EXCEPT AS STATED ABOVE.

In no event shall SYNGENTA or Seller be liable for any incidental, consequential or special damages resulting from the use or handling of this product. **THE EXCLUSIVE REMEDY OF THE USER OR BUYER, AND THE EXCLUSIVE LIABILITY OF SYNGENTA AND SELLER FOR ANY AND ALL CLAIMS, LOSSES, INJURIES OR DAMAGES (INCLUDING CLAIMS BASED ON BREACH OF WARRANTY, CONTRACT, NEGLIGENCE, TORT, STRICT LIABILITY OR OTHERWISE) RESULTING FROM THE USE OR HANDLING OF THIS PRODUCT, SHALL BE THE RETURN OF THE PURCHASE PRICE OF THE PRODUCT OR, AT THE ELECTION OF SYNGENTA OR SELLER, THE REPLACEMENT OF THE PRODUCT.**

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DIRECTIONS FOR USE

It is a violation of Federal law to use this product in a manner inconsistent with its labeling.

This product may be used ~~only to manufacture/formulate other insecticide products registered and labeled for use on head and stem Brassica vegetables, celery, and head lettuce.~~ *replace w/ text on p1*

STORAGE AND DISPOSAL

Do not store near food or feed. Do not contaminate water, food, or feed by storage or disposal.

Store in a tightly closed original container in a cool, dry place.

Pesticide Disposal

Pesticide wastes are acutely hazardous. Improper disposal of excess pesticide, or rinsate is a violation of Federal law. If these wastes cannot be disposed of by use according to label instructions, contact your State Pesticide or Environmental Control Agency, or the Hazardous Waste representative at the nearest EPA Regional Office for guidance. ~~Pesticide that cannot be used or chemically reprocessed must be disposed of according to federal, state, or local procedures under the Resource Conservation and Recovery Act.~~

Container Disposal

Bulk

Thoroughly clean container before reuse. Consult federal, state, or local disposal authorities for approved alternative procedures.

250 Gal Mini Bulk

This is a refillable container that must be returned to an authorized Syngenta refilling facility for refilling or disposal.

Other Containers

Triple rinse (or equivalent). Then offer for recycling or reconditioning, or puncture and dispose of in a sanitary landfill, or by other procedures approved by state and local authorities.

Note: For minor spills, leaks, etc. follow all precautions indicated on this label and clean up immediately. Take special care to avoid contamination of equipment and facilities during cleanup procedures and disposal of wastes.

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For non-emergency (e.g. current product information)
call Syngenta Crop Protection, Inc. at 1-800-334-9481

Syngenta Crop Protection, Inc.
Greensboro, North Carolina 27409
www.syngenta-us.com

SCP 902A-L1(Draft-A)

Z:LABELE-W/EMATECH902A-L1(DRAFT-A) – ccg – 11/5/01

August 30, 2001 –draft
revised label to EPA,
revised first aid statements
according to PR Notice
2001-1, revised ingredient
statement according to new
CSF and prod. chem,
revised and added storage
and disposal statements,
specified on front panel end-
use product uses supported
for this active ingredient.
Corrected label by adding
Spanish signal word and
warning statement, deleted
chemical name of active –
common name and CAS no.
are sufficient, changed all
references to Novartis to
Syngenta and replaced
Warranty statement with
new Syngenta Warranty
Statement, changed country
of origin to Switzerland,
revised ingredient statement
per PR Notices 97-5 & 97-6
Nov. 5, 2001 – draft –
revised current uses

Z:LABELLE-W/EMATECH902A-L1(DRAFT-A) – ccg – 11/5/01

*Review current use sites and add
pending use sites*

This product may be used only for formulation into an insecticide for the uses listed below (text in parenthesis refers to the general use pattern as referenced in 40CFR158):

1. Agricultural crops (Terrestrial Food Crop)

except cucurbits group
Fruiting vegetables [tomato, eggplant, pepper (includes bell pepper, chili pepper, cooking pepper, pimento, sweet pepper), groundcherry, pepino, tomatillo]; leafy vegetables [Celery, Lettuce (head and leaf), Amaranth, Arugala, Cardoon, Chinese celery, Celtuce, Chervil, Edible-leaved chrysanthemum, Garland chrysanthemum, Corn salad, Garden cress, Upland cress, Dandelion, Dock, Endive, Fennel, Orach, Parsley, Garden purslane, Winter purslane, Radicchio, Rhubarb, Spinach, New Zealand Spinach, Vine Spinach and Swiss chard]; head and stem Brassica Vegetables [Broccoli, Brussels sprouts, Cabbage, Cauliflower, Cavolo broccolo, Chinese broccoli, Chinese (napa) cabbage, Chinese mustard cabbage, Kohlrabi]; and Leafy Brassica Vegetables [Broccoli, Chinese (bok choy) cabbage, Collards, Kale, Mizuna, Mustard greens, Mustard spinach, Rape greens].

2. Agricultural crops (Terrestrial Non-Food)

food feed
Cotton and Tobacco.

3. Uses for which the US EPA has accepted the required data and/or citations of data that the formulator has submitted in support of registration excluding any use strictly prohibited by this label.

4. Uses for experimental purposes that are in compliance with US EPA requirements.

Active Ingredient:

Eamectin Benzoate (CAS No. 155569-91-8) 97.0%

Other Ingredients: 3.0%

Total: 100.0%

KEEP OUT OF REACH OF CHILDREN

SKULL & CROSSBONES]

DANGER/PELIGRO
POISON
[red type]

[SKULL & CROSSBONES]



Si usted no entiende la etiqueta, busque a alguien para que se la explique a usted en detalle. (If you do not understand the label find someone to explain it to you in detail.)

See additional precautionary statements on label.

EPA Reg. No. 100-902
EPA Est. 41448-SW-1

Product of Switzerland

SCP 902A-L1(Draft-B)

Lot# _____
Net Weight: _____
Physical _____ kg
Assay _____ kg
Drum No. _____

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©2001 Syngenta

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SCP 902A-L1(Draft-B)

Z:LABEL-W/EMATECH902A-L1(DRAFT-B) - ccg - 11/5/01

August 30, 2001 –draft
revised label to EPA,
revised first aid statements
according to PR Notice
2001-1, revised ingredient
statement according to new
CSF and prod. chem,
revised and added storage
and disposal statements,
specified on front panel end-
use product uses supported
for this active ingredient.
Corrected label by adding
Spanish signal word and
warning statement, deleted
chemical name of active –
common name and CAS no.
are sufficient, changed all
references to Novartis to
Syngenta and replaced
Warranty statement with
new Syngenta Warranty
Statement, changed country
of origin to Switzerland,
revised ingredient statement
per PR Notices 97-5 & 97-6
November 5, 2001 – Draft
revised current uses and
added uses pending

Z:LABELLE-W/EMATECH902A-L1(DRAFT-B) - ccg – 11/5/01



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MAY 15 2002

John Hott
Syngenta Crop Protection, Inc.
PO Box 18300
Greensboro, NC 27419

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES


re: Enamectin benzoate, OPP pc code 122806
Request to reduce REI from 48 to 12 hours
request denied

Dear Mr. Hott:

Enclosed please find a copy of a 1/16/02 review by Jack Arthur in response to your 6/3/99 request to reduce the re-entry interval (REI) for emamectin benzoate from 48 to 12 hours. EPA does not find that a reduction of the Worker Protection Standard required REI for emamectin benzoate from 48 hours to 12 hours is warranted or justified.

Also, enclosed is a copy of a 5/10/99 review by Steven Weiss on the same subject (and reaching the same conclusion). This was probably sent to you earlier but I have included an extra copy here for your convenience.

Sincerely,


Thomas C. Harris
Insecticide / Rodenticide Branch
Registration Division (7505C)
Office of Pesticide Programs
voice: (703) 308-9423 fax: (703) 305-6596
email: harris.thomas@epa.gov

enclosures



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

January 16, 2002

MEMORANDUM

SUBJECT: Response to Novartis' Request to Reduce Emamectin Benzoate Restricted Entry Interval from 48 Hours to 12 Hours (DP Barcode No. D265289; MRID 440079-03)

FROM: *Jack Arthur*
Jack Arthur, Environmental Scientist
Registration Action Branch 3
Health Effects Division (7509C)

TO: Tom Harris, Product Manager
Insecticide-Rodenticide Branch
Registration Division (7505C)

THRU: Stephen Dapson, BSS *Stephen C. Dapson*
Registration Action Branch 3
Health Effects Division (7509C) *01/24/2002*

On June 3, 1999, OPP received from Novartis Crop Protection, Inc., a document entitled, "Emamectin Benzoate: PP No. 6F4628: Proclaim™, EPA Reg. No. 100-904, Rationale for a 12-Hour Re-Entry Interval (REI)." A previous submission by Novartis, which also proposed a 12-hour REI for emamectin, had been reviewed by HED (Memo from Steven Weiss to Arnold Layne/Linda Arrington, March 10, 1999). Based on the March 10th review, HED concluded that a 48-hour REI is required for emamectin products. Likewise, based on a review of the current Novartis' proposal, **HED still does not believe that a reduction of the WPS-required REI for emamectin benzoate from 48 hours to 12 hours is warranted or justified.**

In its June 3, 1999 submission, Novartis presented its proposal for establishment of a 12-hour REI in three major parts:

- *"Using DFR data, primary eye irritation data and conservative assumptions, Novartis has calculated a 'Tier 1' assessment for ocular exposure and risk. The assessment demonstrates a large margin of safety for Proclaim even at 0-hours after application."*
- *"The use of Proclaim will overall increase worker safety when it replaces toxic insecticides, such as organophosphates, that result in much larger exposures and lower margins of safety."*
- *"Low contact and low exposure characterize re-entry activities that will occur in the field between 12 and 48-hours after application."*

Each section of the Novartis proposal is presented separately below, followed by HED comments. HED's overall conclusions are presented at the very end.

Novartis Proposal:

Re-entry Dermal Exposure

Novartis uses the day "0" residue levels (0.00473 ug/cm^2) found in a DFR study performed with emamectin on celery (MRID 440079-03), and a transfer coefficient for scouting and irrigation ($1000 \text{ cm}^2/\text{hr}$) to calculate a postapplication dose of $5.4\text{E-}4 \text{ mg/kg/day}$. It compares this exposure to the NOAEL of $22.1 \text{ mg ai/kg/day}$ from a 21-day rabbit dermal toxicity study (MRID 42743625) to show an MOE of nearly 41,000 for day-zero postapplication dermal risk.

HED Comment:

The celery DFR study referenced by Novartis was reviewed by HED and the results used in its occupational exposure and risk assessment for the petition to use emamectin on cotton, fruiting vegetables, leafy vegetables and tobacco. HED corrected values in the study for field recovery, so that the day "0" residue level used by Novartis (0.00473 ug/cm^2), was corrected to 0.00591 ug/cm^2 . The transfer coefficients used in HED's assessment are from an interim transfer coefficient policy developed by HED's Science Advisory Council for Exposure using proprietary data from the Agricultural Re-entry Task Force (ARTF) database (policy # 3.1). Transfer coefficients for scouting and irrigation for applicable crops range as high as $1500 \text{ cm}^2/\text{hr}$. For other activities such as hand-weeding and thinning, the transfer coefficients range up to $2500 \text{ cm}^2/\text{hr}$. HED's Hazard Identification Assessment Review Committee (HIARC) selected a neurotoxicity endpoint from a 15-day oral mouse study (NOAEL = 0.075 mg/kg/day) as the most appropriate for emamectin. Using this endpoint, as well as results from the celery DFR study and ARTF transfer coefficients, HED calculated MOEs for scouting and irrigation on day "0" that ranged as low as 4100, and for thinning, as low as 2500. These postapplication dermal risks are all above 100, and, therefore, are not of concern to HED.

While Novartis' conclusions regarding the risk for day "0" postapplication dermal exposures are similar to those of HED (i.e., MOEs are different, but all are above 100, and therefore not of concern), dermal risk is determined by a systemic toxicity endpoint where a dose-response has been established for a carefully selected toxicity endpoint. The dermal risk determined in such a way is not relevant to concern for the acute eye irritation potential of emamectin.

Novartis Proposal:

Ocular Effects Benchmark

Novartis points to acute eye irritation test results to conclude that the "severity of the irritation reaction in rabbit eye is clearly related to the amount of the test material administered." They report the results of (MRID 42743615), where the administration of technical product to rabbit eyes (28 mg of emamectin) caused severe eye irritation and irreversible changes after 21 days of observation (Toxicity Category I). Novartis also points to a primary acute eye irritation study (MRID 43824005), where a formulated granular end-use product (5 mg of emamectin) resulted in slight eye irritation, which was completely reversible within seven days (Toxicity Category III). Novartis uses this latter test result as an ocular effects benchmark for a 12-hour REI.

HED Comment:

The relevance of acute eye irritation caused by an end-use product versus that caused by the active ingredient alone, is always questionable. When a formulated product is used in an acute eye irritation study, it is not possible to know the exact contribution the carrier makes to the effects seen. It is reasonable to assume that a carrier such as hexanol would contribute to eye irritation, in synergy with, or independent from, the active ingredient. Whereas, it is possible that a granular formulation might actually mitigate the irritation that would otherwise be caused by an active ingredient alone. For these reasons, HED does not believe it is appropriate to use the results of an acute eye irritation study with a formulated product to deduce the irritation effect of the active ingredient alone. This is why the Agency uses the results from acute eye irritation tests with the technical active ingredient as an index of hazard from postapplication exposure, where exposure to the active ingredient alone is most likely. This also is why the Agency uses the results from acute eye irritation tests with the formulated product as an index of hazard from handler exposure, where potential toxic effects from the end-use product are of concern.

Novartis Proposal:

Re-entry Eye Exposure

Novartis assumes that the most likely route of eye exposure to postapplication workers will be from hand-to-eye. Total body exposure was calculated by multiplying the estimated re-entry dermal dose (5.4×10^{-4} mg/kg/day) by a 70 kg body weight, yielding 0.0378 mg of emamectin exposure on day-zero. Novartis further assumes that this entire amount is distributed on the hands. Novartis then assumes that if a worker would transfer 50% of the amount from one hand to one eye, 0.00945 mg of emamectin would be deposited in the eye. Novartis points out that this is approximately 3 orders of magnitude less than the dose that would result in a slight effect (referring to the above referenced eye irritation study where slight irritation was seen with application of 5 mg emamectin in a formulated granular product). Using this approach, Novartis presents MOEs for eye irritation for exposures found from the celery DFR study (using a $T_c = 1000$) at each sampling period (i.e., hours: 0, 4, 8, 12, 24 and 48). MOEs ranged from 528 at zero-hour, to 4457 at 48 hours postapplication. Novartis uses the same approach, but making the assumption that 50% of the total dermal dose is located on the hands and that 20% of this amount is transferred to the eyes, yielding MOEs that range from 2641 at zero-hour, to 22,286 at 48 hours postapplication. In conclusion, Novartis points out that in order to get 5 mg of emamectin into the eyes of postapplication workers, either 1500% of the applied rate would have to be dislodged from the plants, or the worker would have to work for 4500 hours; both of which are not possible. Therefore, Novartis concludes that it is highly unlikely that any eye irritation due to pesticide residues will arise in humans re-entering fields that have been sprayed with emamectin at the 0.015 lb ai/acre rate.

HED Comment:

HED agrees that most eye exposure would come from the hands, although some might be expected from facial sweating, and directly from foliage. HED also agrees that the assumption that the total predicted dermal dose is found on the hands with 50% from one hand being deposited in one eye, is conservative. However, a disagreement by HED arises over the proposal to determine MOEs for eye irritation by using the results from a one-dose application of a formulated end-use product. The determination of an MOE depends upon the results of tests where a dose-response (i.e., tests where multiple doses have been administered) has been established. Endpoints for use in calculating an MOE are based on lowest-observed-adverse-effect-levels (LOAELs) and no-observed-adverse-effect-levels (NOAELs). Using the results of a one-dose test (even if the dose used results in a "benchmark" acute toxicity category III rating) does not show whether the same effect would be seen at a much lower dose.

Novartis Proposal:

Novartis says that a 48-hour REI puts its emamectin products in the same category with several organophosphate and carbamate insecticides. Novartis claims that under this circumstance, growers will likely choose an organophosphate or carbamate because these latter products are cheaper than emamectin, and because they are less selective than emamectin. Novartis points out that many of the organophosphates and carbamates have unacceptable MOEs, while it has shown (including by EPA) that emamectin has wide margins of safety. Novartis states that its emamectin products, Proclaim and Denim, if given a 12-hour REI, are projected to replace a substantial amount of the use of organophosphate and carbamate products. Novartis provides a table of the numbers of acres treated by "less safe" products, e.g., endosulfan, chlorpyrifos and methomyl, and the projected reduction in this use resulting from substitution by emamectin products. Most of the products listed have 24- or 48-hour REIs.

HED Comment:

It is important to apply a consistent methodology for evaluating all active ingredients. The organophosphates (OPs) and carbamates listed by Novartis are all subject to the same criteria and assessment methodologies as emamectin. The Novartis listing of WPS-established REIs for various OPs and carbamates does not show the entire picture for comparison with emamectin. A large number of OPs, for instance, have long REIs (in terms of weeks), based on an analysis of systemic toxicity and postapplication exposure. The longest REIs from either the acute toxicity (under WPS) or from an analysis of systemic toxicity are used for label restrictions. In this regard, a 48-hour REI for emamectin may actually be a relatively short period compared to many of the organophosphates and carbamates.

Novartis Proposal:

Novartis points out that because the pre-harvest interval for the emamectin products is 7 days, only low exposure activities such as thinning, weeding, moving irrigation pipes and applying fertilizers would occur during the 12- to 48-hour period following application. They further point out that thinning, hand-weeding and irrigation activities fall into the ARTF's cluster of categories associated with small contact regarding broccoli and lettuce. Novartis states that these categories, while subjective, give a relative indication that thinning, weeding and moving irrigation pipes for these crops are not high contact activities.

HED Comment:

The ARTF cluster is based more on whole-body exposure, rather than hand exposure. The activities of weeding, thinning and moving irrigation pipes are likely to have very similar hand exposure to harvesting. This point is only relevant when considering the hand-to-eye exposure assessment proposed by Novartis. It is also possible for direct eye contact with treated foliage, and facial sweating to contribute to the hand-to-eye exposure.

Norvartis Conclusions:

Novartis states that it has justified the establishment of a 12-hour REI for emamectin products subject to its petition by the following:

- Novartis has demonstrated a reasonable and conservative method to assess ocular risk due to re-entry activities.
- Proclaim has wide margins of safety with respect to re-entry ocular exposure and risk immediately following application.
- The increased use of Proclaim due to a 12-hour REI will displace other products that have worker exposure issues.
- The activities performed between 12 and 48 hour after application are low contact and result in low exposure.

HED Conclusions:

- HED does not concur with Novartis' methodology for assessing ocular risk from re-entry activities. The use of a "benchmark" dose chosen from an acute study with an end-use product to develop an MOE for postapplication ocular risk is not acceptable for reasons stated in previous sections of this memo.
- HED does not believe that a 12-hour REI alone, will cause Proclaim to displace other products that have worker exposure issues. Many of these other products referred to by the registrant have REIs much longer than 24 or 48 hours, resulting from postapplication risk assessments based on short- and intermediate-term toxicity endpoints.
- HED does not agree that the activities listed by Novartis as low contact (i.e., weeding, pruning and moving irrigation pipes), are actually low contact when specifically considering hand contact. This is important because the registrant's methodology for assessing ocular risk only considers hand-to-eye contact.
- HED is concerned about reducing the WPS-required REI because emamectin is a neurotoxicant. In EPA's Pesticide Regulation (PR) Notice 95-3, "Reduction of Worker Protection Standard (WPS) Interim Restricted Entry Intervals (REIs) for Certain Low Risk Pesticides," certain criteria must be met in order to reduce an REI from 12 hours to 4 hours. One of these criterion is that, "No known reproductive, developmental, carcinogenic, or neurotoxic effects have been associated with the active ingredient." The registrant is requesting a reduction of the current WPS-required 48-hour REI to a 12-hour REI, and HED believes that same criteria should apply to this determination.

In summary, **HED does not believe that a reduction of the WPS-required REI for emamectin benzoate from 48 hours to 12 hours is warranted or justified.**



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND
TOXIC SUBSTANCES

03/SEPT/1999

MEMORANDUM

Dislodgeable foliar residue protocol re. REI

Subject: File Symbol/EPA Reg. No.: 100-904 Proclaim 5 SG Insecticide
DP Barcode: D256650 *5563186*
Case No: 039944
PC Code: 122806

File Symbol/EPA Reg. No.: 100-903 Proclaim 0.16 EC Insecticide
DP Barcode: D256721 *5563354*
Case No: 039877
PC Code: 122806

From: Eugenia McAndrew, Biologist *Em*
Technical Review Branch *JCB*
Registration Division (7505C)

To: Thomas Harris, PM Team 04
Insecticide-Rodenticide Branch
Registration Division (7505C)

Applicant: Novartis Crop Protection, Inc.
P.O. Box 18300
Greensboro, NC 27419-8300

ACTION REQUESTED: PM requests review of registrant's arguments in favor of reducing REI for EPA Reg. Nos. 100-904 and 100-903.

BACKGROUND: Novartis Crop Protection, Inc. requested a reduction in the Restricted Entry Interval (REI) for EPA Reg. No. 100-904, Proclaim 0.16 EC Insecticide. The request was denied by HED in May of 1999. Novartis has presented additional information in favor of a 12-hour REI for Agency consideration.

RECOMMENDATIONS: This is basically an HED matter. In general, TRB uses the toxicity categories of the product(s) to determine the REI as detailed in the Label Review Manual on pages 11-15 to 11-19. However, in this case, HED risk assessments may identify endpoints of concern which could affect the determination of the REI. Therefore, it is appropriate for HED to make the decision regarding the REI.



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

Date: 5/10/99

Subject: HED's Response to Novartis Request to Reduce Proclaim's REI from 48 Hours to 12 Hours.

| | | | |
|-------------|---------|-------------|-------------|
| Chemical #: | 122806 | Class: | Insecticide |
| DP Barcode: | D254469 | Trade Name: | Proclaim |
| PRAT Case#: | 287173 | EPA Reg. #: | N/A |

To: Arnold Layne/Linda Arrington PM 03
Insecticide-Rodenticide Branch
Registration Division (7505C)

From: Steven Weiss, Industrial Hygienist
Health Effects Division/Registration Action Branch 2 (7509C)

Thru: Richard Loranger, Branch Senior Scientist
Health Effects Division/Registration Action Branch 2 (7509C)

INTRODUCTION

HED has been asked to comment on Novartis' request to reduce the restricted-entry interval (REI) for the products with the tradename Proclaim (active ingredient emamectin) to 12 hours. This request from the registrant is associated with the use of emamectin on various leafy/Brassica vegetables, for which HED recently completed a human health risk assessment (4/6/99, Barcode D241907). In that document it was concluded that a 48-hour REI is needed to comply with the Worker Protection Standard (WPS).

CONCLUSION

HED continues to conclude that a 48-hour REI is required for the Proclaim products. Our responses to each of Novartis' rationales are detailed in Table 2.

DETAILED CONSIDERATIONS

The Environmental Protection Agency's requirements regarding Restricted-entry Intervals (REIs) is included in CFR 156.208. Guidance on applying these requirements are also included in Chapter 11 of the Office of Pesticide Programs' Label Review Manual.

Per CFR 156.208, REIs are based on the most severe acute toxicity category assigned to the acute dermal, eye irritation and skin irritation data for all of the active ingredients (a.i.) in a

product. A 48 hour REI is established for any product containing an active ingredient in Toxicity Category I (highly toxic). An REI of 48 hours for organophosphates is extended to 72 hours if these products are applied outdoors in areas with less than 25 inches of rainfall per year. A 24 hour REI is established for any product containing an active ingredient in Toxicity Category II. A 12 hour REI is established for all other products. An 4 hour REI is sometimes permitted for products meeting strict criteria for low risk.

The EPA considers the REI established under the requirements in CFR 156.208 as an "interim" until a review of entry residue exposure data (with toxicity endpoints) is completed during the reregistration (and registration) process. However, the Agency has no mechanism for using the skin and eye irritation toxicity categories to determine an appropriate REI. Currently, only the endpoint for dermal toxicity is used to assess risk with respect to postapplication exposures. Until an appropriate mechanism is found for using skin and eye irritation potentials as an endpoint to assess possible risk with respect to postapplication exposures, the WPS interim REI remains in effect for those two triggers. Hence, even when a postapplication analysis is completed using the dermal toxicity endpoint, the REI adopted for the product is the more severe REI between that analysis and the WPS defaults for skin and eye irritation categories.

The end-use product Proclaim contains one active ingredient, emamectin. The acute toxicity categories for emamectin technical material are summarized in Table 1.

| Guideline No. | Study Type | MRID# | Results | Toxicity Category |
|----------------------|-----------------------------------|--------------|---|--------------------------|
| 870.1100 | Acute Oral- Rats | 42851519 | LD ₅₀ for L-656,748-038 = 53 mg/kg | 2 |
| 870.1200 | Acute Dermal- Rabbits | 43850111 | LD ₅₀ > 2.0 mg/kg | 3 |
| 870.1300 | Acute Inhalation- Rats | 43868101 | LC ₅₀ 0.10 mg/L | 4 |
| 870.2400 | Primary Eye Irritation- Rabbits | 42743615 | Severe irritation | 1 |
| 870.2500 | Primary Skin Irritation- Rabbits | 42743616 | No dermal irritation | 4 |
| 870.2600 | Dermal Sensitization- Guinea pigs | 42743617 | Not a dermal sensitizer | - |

As shown in Table 1, emamectin has a Toxicity Category 1 for primary eye irritation. Therefore, an REI of 48-hours is required by the WPS.

A summary of HED's responses to Novartis' rationale for reducing the REI from 48 to 12 hours (letter dated March 16, 1999) is included in Table 2.

Table 2. HED's Responses to Novartis' Rationale for Reducing the REI from 48 to 12 hours

| Novartis' rationale | HED's Response |
|---|--|
| <p><i>The 48-hour REI is based on the toxicity of the technical material and does not take in to account the rate or use characteristics of the end-use product.</i></p> | <p>Using the toxicity of the technical material for the purposes of establishing and REI and not taking in to account the rate or use characteristics of the end-use product is consistent with the requirements of the WPS. The use characteristics of the end-use product are not used to determine the REI. The rationale for this is that the toxicity categories of the end-use product, particularly with respect to skin and eye irritation potential is often based on characteristics of inert ingredients, such as xylene, that would no longer be present in the residue remaining on a treated surface. Also, an end-use product concentrate might have higher toxicity categories than a ready-to-use product with the same active ingredient, but they could be applied at the same rate per acre. EPA is concerned about the toxicological characteristics of the residue remaining after an application is complete and any volatile components have dissipated. Usually, that is the active ingredient.</p> |
| <p><i>HED overlooked chemical specific post-application data that were submitted in support of the registration. Two volumes have been submitted concerning postapplication exposure: a risk assessment for postapplication exposure and a dislodgeable foliar residue study.</i></p> | <p>No exposures studies were provided to HED/RAB2 in support of the registration. Default values were used to estimate exposures and risk during postapplication activities.</p> <p>HED's risk estimates for dermal exposure during postapplication activities were based short- and intermediate-term dermal endpoint from a 15-day oral mouse study. The short-term endpoint was based on tremors on day 3 of dosing, whereas the intermediate endpoint was based on moribund sacrifices, clinical signs of neurotoxicity, decreases in body weight and food consumption and histopathological lesions in the sciatic nerve. HED concluded that the MOEs on the day of application are acceptable but this relates only to the short- and intermediate-term dermal endpoints and does not take into account eye exposure.</p> <p>Furthermore, the EPA does not consider only dermal exposure when establishing REIs. As stated in the Federal Register/Vol 57, No 163, page 38110 on 8/21/92, the EPA did consider using only dermal toxicity to establish REIs, but the potential for eye and skin irritation and for respiratory exposure may be significant in some situations. Cases of eye irritation are four times as common as those from systemic poisonings among re-entering workers.</p> |

Table 2. HED's Responses to Novartis' Rationale for Reducing the REI from 48 to 12 hours

| Novartis' rationale | HED's Response |
|--|---|
| <i>Worker Exposure risk assessments for re-entry demonstrate a reasonable certainty of no harm with a 12-hour REI</i> | Worker exposure risk assessments for re-entry demonstrate a reasonable certainty that the <i>dermal</i> endpoint of concern will not cause unacceptable risk with a 12-hour REI. These assessments do not relate to the potential for eye and skin irritation |
| <i>Cole crops and leafy vegetables require constant tending during the proclaim use season. A 48-hour REI would severely compromise the utility of proclaim.</i> | If cole crops and leafy vegetables require constant tending during the proclaim use season and enamectin is a severe eye irritant, it seems reasonable to assume that there may be a potential eye hazard. Evidence gathered during the comment period leading to promulgation of the WPS and more recently indicates that no <i>hand labor tasks</i> related to cole crops and leafy vegetables are time-sensitive to the degree that a 48-day delay would disrupt crop production or cause significant economic loss. |

Table 2. HED's Responses to Novartis' Rationale for Reducing the REI from 48 to 12 hours

| Novartis' rationale | HED's Response |
|---|--|
| <p><i>Novartis states that a 12-hour REI is needed to due hand labor demands associated crop. During the use season for proclaim, growers need to be able re-enter the fields constantly to scout for pests, weed, cull, and irrigate crops.</i></p> <p><i>IRRIGATION HAS BEEN GIVEN 8 HRS OR EARLY ENTRY</i> <i>OK</i></p> | <p>The WPS currently allows entry into areas that remain under an REI to perform scouting tasks. Under the WPS, scouts are considered pesticide handlers and can enter treated areas without regard to the REI, provided specified conditions are met.</p> <p>The WPS currently allows entry into areas that remain under an REI to perform short-term tasks, (such as irrigation tasks,) provided (1) no hand labor activity is performed, (2) the time in treated areas under a restricted-entry interval for any worker does not exceed 1 hour in any 24-hour period, and (3) other specified conditions, such as wearing personal protective equipment required for early entry, are met.</p> <p>In addition, the WPS (1995 amendment) allows entry during a restricted-entry for up to 8 hours in a 24-hour period to perform irrigation tasks, provided (1) the tasks could not have been foreseen and which, if delayed, would cause significant economic loss, (2) contact with treated surfaces is minimal, (3) early-entry personal protective equipment is worn, and (4) other specified conditions are met. However, this exception probably could not be used for this pesticide, since <u>clearly irrigation tasks have been foreseen.</u></p> <p>During the entire notice and comment period leading up to the 1992 Worker Protection Standard and its 1995 amendments, EPA received no convincing evidence that hand labor tasks involving weeding and culling were time sensitive to the degree that a 48-day delay would disrupt crop production or cause significant economic loss.</p> <p><i>but perhaps not the need to treat w/ the product.</i></p> |

Table 2. HED's Responses to Novartis' Rationale for Reducing the REI from 48 to 12 hours

| Novartis' rationale | HED's Response |
|--|---|
| <p><i>Also submitted was an exposure assessment prepared by Jellinek, Schwartz, & Connolly, Inc (MRID 43943301). This assessment cited the Merck celery dislodgeable study and concurred with Agency's assessment of dermal exposure being safe after spray dries.</i></p> | <p>The requirement of not letting agricultural workers enter fields until "sprays have dried, dust have settled, vapors have dispersed" was replaced by the requirements of the WPS in 1992. Furthermore, the assessment concurred with EPA's assessment that <i>dermal</i> exposure was safe after spray dries. No evidence was presented or cited to indicate that <i>ocular</i> exposure was safe.</p> |
| <p><i>The use rate for proclaim is a very low 0.015 lb ai/A which results in low dislodgeable residues which are measures in picograms. The low availability of residues for transfer to skin and eyes demonstrates that a the requirement for 48-hour reentry is not warranted.</i></p> | <p>EPA recognizes that there is no currently available mechanism for assessing the impact of postapplication exposures relative to skin or eye irritation effects. Until such a mechanism is in place, the Agency believes it prudent to rely on the default WPS REIs that were established through a notice-and-comment rulemaking process. EPA notes that a large percentage of postapplication worker poisoning incidents are due to skin and eye irritation. It also notes that risk is related to both toxicity and exposure. If a product is highly irritating, a relatively small exposure could result in adverse effects. The Agency welcomes the submission of possible mechanisms for determining REIs based on skin and eye irritation potential.</p> |

DP BARCODE: D265289

CASE: 039877
SUBMISSION: S563354

DATA PACKAGE RECORD
BEAN SHEET

DATE: 04/20/00
Page 1 of 2

* * * CASE/SUBMISSION INFORMATION * * *

CASE TYPE: REGISTRATION ACTION: 352 PROP TEST PROT-AMND
RANKING : 20 POINTS ()
CHEMICALS: 122806 4''-Epimethylamino-4''-deoxyavermectin B1a and B1b 2.1500%

ID#: 000100-00903 PROCLAIM 0.16 EC INSECTICIDE
COMPANY: 000100 NOVARTIS CROP PROTECTION, INC.
PRODUCT MANAGER: 04 TINA LEVINE 703-308-7055 ROOM: CM2 219
PM TEAM REVIEWER: THOMAS HARRIS 703-308-9423 ROOM: CM2 211
RECEIVED DATE: 06/03/99 DUE OUT DATE: 09/21/99

* * * DATA PACKAGE INFORMATION * * *

DP BARCODE: 265289 EXPEDITE: N DATE SENT: 04/20/00 DATE RET.: / /
CHEMICAL: 122806 4''-Epimethylamino-4''-deoxyavermectin B1a and B1b benzoate
DP TYPE: 001

| | CSF: N | | LABEL: N | |
|-------------|--------|----|----------|-----|
| ASSIGNED TO | DATE | IN | DATE | OUT |
| DIV : HED | / | / | / | / |
| BRAN: RAB3 | / | / | / | / |
| SECT: IO | / | / | / | / |
| REVR : | / | / | / | / |
| CONTR: | / | / | / | / |

ADMIN DUE DATE: 06/29/00
NEGOT DATE: / /
PROJ DATE: / /

* * * DATA REVIEW INSTRUCTIONS * * *

- 1) MRID 440079-03
- 2) 5/20/99 Novartis letter: rationale for 12-hr REI

to: JACK ARTHUR
se also: beans to Jonathan Becker (D256726)
Kathy Raffaele (D265288)

Novartis has proposed a rationale for reducing REI's using dislodgeable foliar residues. This submission is specifically for emamectin (100-903 and 100-904) but logic could apply to other chemicals.

Jonathan Becker has copy of 5/20/99 Novartis letter to take to EXPOSAC. As input to this, he has requested that the reference eye irritation study (MRID 427436-15) and the dislodgeable foliar residue study (MRID 440079-03) be reviewed (or copies of previous reviews found).

JACK: Please review enclosed dislodgeable foliar residue study (or find previous review). You may want to consult with Kathy Raffaele who is reviewing the eye irritation study.

RESULTS SHOULD BE GIVEN TO BOTH ME AND JONATHAN BECKER.

DP BARCODE: D265289

CASE: 039877
SUBMISSION: S563354

DATA PACKAGE RECORD (CONTINUED)
BEAN SHEET

DATE: 04/20/00
Page 2 of 2

* * * DATA REVIEW INSTRUCTIONS * * *

Thanks.

-Tom Harris
RD/IRB
308-9423

* * * DATA PACKAGE EVALUATION * * *

No evaluation is written for this data package

* * * ADDITIONAL DATA PACKAGES FOR THIS SUBMISSION * * *

| DP BC | BRANCH/SECTION | DATE OUT | DUE BACK | INS | CSF | LABEL |
|--------|----------------|----------|----------|-----|-----|-------|
| 256721 | TRB/TOX | 06/09/99 | 08/18/99 | Y | Y | Y |
| 256723 | RAB2/IO | 06/09/99 | 08/18/99 | Y | Y | Y |
| 256726 | RRB2/IO | 06/09/99 | 08/18/99 | Y | Y | Y |
| 265288 | RAB3/IO | 04/20/00 | 06/29/00 | Y | N | |

DP BARCODE: D265288

CASE: 039877
SUBMISSION: S563354

DATA PACKAGE RECORD
BEAN SHEET

DATE: 04/20/00
Page 1 of 2

* * * CASE/SUBMISSION INFORMATION * * *

CASE TYPE: REGISTRATION ACTION: 352 PROP TEST PROT-AMND
RANKING : 20 POINTS ()
CHEMICALS: 122806 4''-Epimethylamino-4''-deoxyavermectin B1a and B1b 2.1500%
ID#: 000100-00903 PROCLAIM 0.16 EC INSECTICIDE
COMPANY: 000100 NOVARTIS CROP PROTECTION, INC.
PRODUCT MANAGER: 04 TINA LEVINE 703-308-7055 ROOM: CM2 219
PM TEAM REVIEWER: THOMAS HARRIS 703-308-9423 ROOM: CM2 211
RECEIVED DATE: 06/03/99 DUE OUT DATE: 09/21/99

* * * DATA PACKAGE INFORMATION * * *

DP BARCODE: 265288 EXPEDITE: N DATE SENT: 04/20/00 DATE RET.: / /
CHEMICAL: 122806 4''-Epimethylamino-4''-deoxyavermectin B1a and B1b benzoate
DP TYPE: 001

| ASSIGNED TO | CSF: N | DATE | IN | LABEL: | DATE OUT | ADMIN DUE DATE: 06/29/00 |
|-------------|--------|------|----|--------|-------------|--------------------------|
| DIV : HED | | / | / | | 1 / 24 / 00 | NEGOT DATE: / / |
| BRAN: RAB3 | | / | / | | / / | PROJ DATE: / / |
| SECT: IO | | / | / | | / / | |
| REVR : | | / | / | | / / | |
| CONTR: | | / | / | | / / | |

* * * DATA REVIEW INSTRUCTIONS * * *

- 1) MRID 427436-15
- 2) 5/20/99 Novartis letter: rationale for 12-hr REI

to: KATHY RAFFAELE
see also: beans to Jonathan Becker (D256726)
Jack Arthur (D#tbd)

Novartis has proposed a rationale for reducing REI's using dislodgeable foliar residues. This submission is specifically for emamectin (100-903 and 100-904) but logic could apply to other chemicals.

Jonathan Becker has copy of 5/20/99 Novartis letter to take to EXPOSAC. As input to this, he has requested that the referenced eye irritation study (MRID 427436-15) and the dislodgeable foliar residue study (MRID 440079-03) be reviewed (or copies of previous reviews found).

KATHY: Please review enclosed eye irritation study done on technical emamectin (or find previous review). Read Novartis letter to see if you think other studies should be input on this issue. They do reference another eye study (p. 4) but do not provide MRID. You may want to talk w/ Jack Arthur who will receive a similar bean for the DFR study.

DP BARCODE: D265288

CASE: 039877 DATA PACKAGE RECORD (CONTINUED)
SUBMISSION: S563354 BEAN SHEET

DATE: 04/20/00
Page 2 of 2

* * * DATA REVIEW INSTRUCTIONS * * *

RESULTS SHOULD BE GIVEN BOTH TO ME AND TO JONATHAN BECKER.
Thanks.

-Tom Harris
RD/IRB
308-9423

* * * DATA PACKAGE EVALUATION * * *

No evaluation is written for this data package

* * * ADDITIONAL DATA PACKAGES FOR THIS SUBMISSION * * *

| DP BC | BRANCH/SECTION | DATE OUT | DUE BACK | INS | CSF | LABEL |
|--------|----------------|----------|----------|-----|-----|-------|
| 256721 | TRB/TOX | 06/09/99 | 08/18/99 | Y | Y | Y |
| 256723 | RAB2/IO | 06/09/99 | 08/18/99 | Y | Y | Y |
| 256726 | RRB2/IO | 06/09/99 | 08/18/99 | Y | Y | Y |

DP BARCODE: D256726

CASE: 039877
SUBMISSION: S563354

HED
finished under
D 265289
close D 256726
1/29/02
6/9/99
DATA PACKAGE RECORD
BEAN SHEET

DATE: 06/09/99
Page 1 of 1

*** CASE/SUBMISSION INFORMATION ***

CASE TYPE: REGISTRATION ACTION: 352 PROP TEST PROT-AMND
RANKING : 5 POINTS ()
CHEMICALS: 122806 4''-Epimethylamino-4''-deoxyavermectin B1a and B1b 2.1500%

ID#: 000100-00901 PROCLAIM 0.16 EC INSECTICIDE
COMPANY: 000100 NOVARTIS CROP PROTECTION, INC.
PRODUCT MANAGER: 04 TINA LEVINE 703-308-7055 ROOM: CM2 219
PM TEAM REVIEWER: THOMAS HARRIS 703-308-9423 ROOM: CM2 211
RECEIVED DATE: 06/03/99 DUE OUT DATE: 09/21/99

*** DATA PACKAGE INFORMATION ***

DP BARCODE: 256726 EXPEDITE: N DATE SENT: 06/09/99 DATE RET.: / /
CHEMICAL: 122806 4''-Epimethylamino-4''-deoxyavermectin B1a and B1b benzoate
DP TYPE: 001

CSF: Y LABEL: Y
ASSIGNED TO DATE IN DATE OUT ADMIN DUE DATE: 08/18/99
DIV : HED 6/9/99 6/9/99 NEGOT DATE: / /
BRAN: IO / / PROJ DATE: / /
SECT: IO / /
REVR : / /
CONTR: / /

*** DATA REVIEW INSTRUCTIONS ***

~~to Johnathan Becker~~ ~~also tracked under D256645~~ *will delete this*
Please review Novartis proposed method (pinpunched 6/3/99) to reduce REI when it is based on eye irritation. Current protocol results in REI of 48 hours; Novartis says their method would support 12 hours. If approved, this methodology could also be used for other chemicals as well as current product (emamectin, #100-903). This is also being sent to Steve Weiss (HED) and John Redden (RD/tox). If questions call Tom Harris, 308-9423, rm 213 CM2. Thanks.

*** DATA PACKAGE EVALUATION ***

No evaluation is written for this data package

*** ADDITIONAL DATA PACKAGES FOR THIS SUBMISSION ***

| DP BC | BRANCH/SECTION | DATE OUT | DUE BACK | INS | CSF | LABEL |
|--------|----------------|----------|----------|-----|-----|-------|
| 256721 | TRB/CHEM | 06/09/99 | 08/18/99 | Y | Y | Y |
| 256723 | IO/IO | 06/09/99 | 08/18/99 | Y | Y | Y |

DP BARCODE: D256721

CASE: 039877
SUBMISSION: S563354

DATA PACKAGE RECORD
BEAN SHEET

DATE: 06/09/99
Page 1 of 1

* * * CASE/SUBMISSION INFORMATION * * *

CASE TYPE: REGISTRATION ACTION: 352 PROP TEST PROT-AMND
RANKING : 5 POINTS ()
CHEMICALS: 122806 4''-Epimethylamino-4''-deoxyavermectin Bla and Blb 2.1500%
ID#: 000100-00903 PROCLAIM 0.16 EC INSECTICIDE
COMPANY: 000100 NOVARTIS CROP PROTECTION, INC.
PRODUCT MANAGER: 04 TINA LEVINE 703-308-7055 ROOM: CM2 219
PM TEAM REVIEWER: THOMAS HARRIS 703-308-9423 ROOM: CM2 211
RECEIVED DATE: 06/03/99 DUE OUT DATE: 09/21/99

* * * DATA PACKAGE INFORMATION * * *

DP BARCODE: 256721 EXPEDITE: N DATE SENT: 06/09/99 DATE RET.: / /
CHEMICAL: 122806 4''-Epimethylamino-4''-deoxyavermectin Bla and Blb benzoate
DP TYPE: 001

| ASSIGNED TO | CSF: Y | DATE | IN | LABEL: Y | DATE OUT | ADMIN DUE DATE: 9 8 99 |
|-----------------------|--------|------|----|----------|----------|------------------------|
| DIV : RD | | / | / | | / | / |
| BRAN: TRB | | / | / | | / | / |
| SECT: CHEM | | / | / | | / | / |
| REVR: 104 | | / | / | | / | / |
| CONTR: | | / | / | | / | / |

* * * DATA REVIEW INSTRUCTIONS * * *

to John Redden: (also tracked under D256650)
Please review Novartis proposed method (pinpunched 6/3/99)
to reduce REI when it is based on eye irritation. Current
protocol results in REI of 48 hours; Novartis says their
method would support 12 hours. If approved, this
methodology could be used for other chemicals as well as
current product (emamectin, # 100-903). This is also being
sent to Johnathan Becker (HED) and Steve Weiss (HED). If
questions call Tom Harris, 308-9423, rm 213 CM2. Thanks.

* * * DATA PACKAGE EVALUATION * * *

No evaluation is written for this data package

* * * ADDITIONAL DATA PACKAGES FOR THIS SUBMISSION * * *

| DP BC | BRANCH/SECTION | DATE OUT | DUE BACK | INS | CSF | LABEL |
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DP BARCODE: D256723

CASE: 039877
SUBMISSION: S563354

*unclassified
beam closed*

DATA PACKAGE RECORD
BEAN SHEET

DATE: 06/09/99
Page 1 of 1

* * * CASE/SUBMISSION INFORMATION * * *

CASE TYPE: REGISTRATION ACTION: 352 PROP TEST PROT-AMND
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PM TEAM REVIEWER: THOMAS HARRIS 703-308-9423 ROOM: CM2 211
RECEIVED DATE: 06/03/99 DUE OUT DATE: 09/21/99

* * * DATA PACKAGE INFORMATION * * *

DP BARCODE: 256723 EXPEDITE: N DATE SENT: 06/09/99 DATE RET.: / /
CHEMICAL: 122806 4'''-Epimethylamino-4'''-deoxyavermectin B1a and B1b benzoate
DP TYPE: 001

CSF: Y LABEL: Y
ASSIGNED TO DATE IN DATE OUT ADMIN DUE DATE: 08/18/99
DIV : HED / / / / NEGOT DATE: / /
BRAN: IO / / / / PROJ DATE: / /
SECT: IO / / / /
REVR : / / / /
CONTR: / / / /

* * * DATA REVIEW INSTRUCTIONS * * *

to Steve Weiss: also tracked under D256646
Please review Novartis proposed method (pinpunched 6/3/99)
to reduce REI when it is based on eye irritation. Current
protocol results in REI of 48 hours; Novartis says their
method would support 12 hours. If approved, this
methodology could be used for other chemicals as well as
current product (emamectin, #100-903). This is also being
sent to Johnathan Becker (HED) and John Redden (RD/tox). If
questions call Tom Harris, 308-9423, rm 213 CM2. Thanks.

* * * DATA PACKAGE EVALUATION * * *

No evaluation is written for this data package

* * * ADDITIONAL DATA PACKAGES FOR THIS SUBMISSION * * *

| DP BC | BRANCH/SECTION | DATE OUT | DUE BACK | INS | CSF | LABEL |
|--------|----------------|----------|----------|-----|-----|-------|
| 256721 | TRB/CHEM | 06/09/99 | 08/18/99 | Y | Y | Y |

DP BARCODE: D256721

CASE: 039877
SUBMISSION: S563354

DATA PACKAGE RECORD
BEAN SHEET

DATE: 02/28/02
Page 1 of 1

* * * CASE/SUBMISSION INFORMATION * * *

CASE TYPE: REGISTRATION ACTION: 352 PROP TEST PROT-AMND
RANKING : 65 POINTS ()
CHEMICALS: 122806 4''-Epimethylamino-4''-deoxyavermectin B1a and B1b 2.1500%

ID#: 000100-00903 PROCLAIM 0.16 EC INSECTICIDE
COMPANY: 000100 SYNGENTA CROP PROTECTION, INC.
PRODUCT MANAGER: 04 TINA LEVINE 703-308-7055 ROOM: CM2 219
PM TEAM REVIEWER: THOMAS HARRIS 703-308-9423 ROOM: CM2 211
RECEIVED DATE: 06/03/99 DUE OUT DATE: 09/21/99

* * * DATA PACKAGE INFORMATION * * *

DP BARCODE: 256721 EXPEDITE: N DATE SENT: 06/09/99 DATE RET.: 09/03/99
CHEMICAL: 122806 4''-Epimethylamino-4''-deoxyavermectin B1a and B1b benzoate
TYPE: 001

CSF: Y LABEL: Y
ASSIGNED TO DATE IN DATE OUT ADMIN DUE DATE: 08/18/99
DIV : RD 06/09/99 09/03/99 NEGOT DATE: 09/08/99
BRAN: TRB 06/10/99 09/03/99 PROJ DATE: / /
SECT: TOX 06/10/99 09/03/99
REVR : EMCANDRE 09/03/99 09/03/99
CONTR: / / / /

* * * DATA PACKAGE EVALUATION * * *

No evaluation is written for this data package

* * * ADDITIONAL DATA PACKAGES FOR THIS SUBMISSION * * *

| DP BC | BRANCH/SECTION | DATE OUT | DUE BACK | INS | CSF | LABEL |
|--------|----------------|----------|----------|-----|-----|-------|
| 256723 | | 06/09/99 | 08/18/99 | Y | Y | Y |
| 256726 | RRB2/IO | 06/09/99 | 08/18/99 | Y | Y | Y |
| 265288 | RAB3/IO | 04/20/00 | 06/29/00 | Y | N | |
| 265289 | RAB3/IO | 04/20/00 | 06/29/00 | Y | N | N |

9179

DP BARCODE: D256650

CASE: 039944
SUBMISSION: S563186

DATA PACKAGE RECORD
BEAN SHEET

DATE: 06/07/99
Page 1 of 1

* * * CASE/SUBMISSION INFORMATION * * *

CASE TYPE: REGISTRATION ACTION: 352 PROP TEST PROT-AMND
RANKING : 5 POINTS ()
CHEMICALS: 122806 4''-Epimethylamino-4''-deoxyavermectin B1a and B1b 5.0000%

ID#: 000100-00904 PROCLAIM 5 SG INSECTICIDE
COMPANY: 000100 NOVARTIS CROP PROTECTION, INC.
PRODUCT MANAGER: 04 TINA LEVINE 703-308-7055 ROOM: CM2 219
PM TEAM REVIEWER: THOMAS HARRIS 703-308-9423 ROOM: CM2 211
RECEIVED DATE: 06/03/99 DUE OUT DATE: 09/21/99

* * * DATA PACKAGE INFORMATION * * *

DP BARCODE: 256650 EXPEDITE: N DATE SENT: 06/07/99 DATE RET.: / /
CHEMICAL: 122806 4''-Epimethylamino-4''-deoxyavermectin B1a and B1b benzoate
DP TYPE: 001

CSF: Y LABEL: Y 9-8-99
ASSIGNED TO DATE IN DATE OUT ADMIN DUE DATE: 08/16/99
DIV : RD / / / / NEGOT DATE: / /
BRAN: TRB / / / / PROJ DATE: / /
SECT: TOX / / / /
REVR : / / / /
CONTR: / / / /

* * * DATA REVIEW INSTRUCTIONS * * *

to JOHN REDDEN:

Please review Novartis proposed method (Pinpunched 6/3/99) to reduce REI when it is based on eye irritation. Current protocol results in REI of 48 hours; Novartis says their method would support 12 hours. If approved, this methodology could be used for other chemicals as well as current product (emamectin, #100-904). This is also being sent to Johnathan Becker (HED) and Steve Weiss (HED). If questions call Tom Harris, 308-9423, rm 213 CM2. Thanks.

* * * DATA PACKAGE EVALUATION * * *

No evaluation is written for this data package

* * * ADDITIONAL DATA PACKAGES FOR THIS SUBMISSION * * *

| DP BC | BRANCH/SECTION | DATE OUT | DUE BACK | INS | CSF | LABEL |
|--------|----------------|----------|----------|-----|-----|-------|
| 256645 | IO/IO | 06/07/99 | 08/16/99 | Y | Y | Y |
| 256646 | IO/IO | 06/07/99 | 08/16/99 | Y | Y | Y |

DP BARCODE: D256645

CASE: 039944
SUBMISSION: S563186

DATA PACKAGE RECORD
BEAN SHEET

DATE: 06/07/99
Page 1 of 1

* * * CASE/SUBMISSION INFORMATION * * *

CASE TYPE: REGISTRATION ACTION: 352 PROP TEST PROT-AMND
RANKING : 5 POINTS ()
CHEMICALS: 122806 4''-Epimethylamino-4''-deoxyavermectin B1a and B1b 5.0000%
ID#: 000100-00904 PROCLAIM 5 SG INSECTICIDE
COMPANY: 000100 NOVARTIS CROP PROTECTION, INC.
PRODUCT MANAGER: 04 TINA LEVINE 703-308-7055 ROOM: CM2 219
PM TEAM REVIEWER: THOMAS HARRIS 703-308-9423 ROOM: CM2 211
RECEIVED DATE: 06/03/99 DUE OUT DATE: 09/21/99

* * * DATA PACKAGE INFORMATION * * *

DP BARCODE: 256645 EXPEDITE: N DATE SENT: 06/07/99 DATE RET.: / /
CHEMICAL: 122806 4''-Epimethylamino-4''-deoxyavermectin B1a and B1b benzoate
DP TYPE: 001

CSF: Y LABEL: Y
ASSIGNED TO DATE IN DATE OUT ADMIN DUE DATE: 08/16/99
DIV : HED / / NEGOT DATE: / /
BRAN: IO / / PROJ DATE: / /
SECT: IO / /
REVR : / /
CONTR: / /

* * * DATA REVIEW INSTRUCTIONS * * *

to JONATHAN BECKER:
Please review Novartis proposed method pinpunched 6/3/99 to reduce REI when based on eye irritation. If approved, this methodology could be used for other chemicals as well as current product (emamectin 100-904). Also being sent to Steve Weiss (HED) and John Redden (RD/tox). If questions call Tom Harris, 308-9423, rm 213 CM2. Thanks.

* * * DATA PACKAGE EVALUATION * * *

No evaluation is written for this data package

* * * ADDITIONAL DATA PACKAGES FOR THIS SUBMISSION * * *

| DP BC | BRANCH/SECTION | DATE OUT | DUE BACK | INS | CSF | LABEL |
|-------|----------------|----------|----------|-----|-----|-------|
|-------|----------------|----------|----------|-----|-----|-------|

DP BARCODE: D25664G

CASE: 039944 DATA PACKAGE RECORD
SUBMISSION: S563186 BEAN SHEET

DATE: 06/07/99
Page 1 of 1

* * * CASE/SUBMISSION INFORMATION * * *

CASE TYPE: REGISTRATION ACTION: 352 PROP TEST PROP-AMND
RANKING : 5 POINTS ()
CHEMICALS: 122806 4''-Epimethylamino-4''-deoxyavermectin B1a and B1b 5.0000%
ID#: 000100-00904 PROCLAIM 5 SG INSECTICIDE
COMPANY: 000100 NOVARTIS CROP PROTECTION, INC.
PRODUCT MANAGER: 04 TINA LEVINE 703-308-7055 ROOM: CM2 219
PM TEAM REVIEWER: THOMAS HARRIS 703-308-9423 ROOM: CM2 211
RECEIVED DATE: 06/03/99 DUE OUT DATE: 09/21/99

* * * DATA PACKAGE INFORMATION * * *

DP BARCODE: 256646 EXPEDITE: N DATE SENT: 06/07/99 DATE RET.: / /
CHEMICAL: 122806 4''-Epimethylamino-4''-deoxyavermectin B1a and B1b benzoate
DP TYPE: 001

CSF: Y LABEL: Y
ASSIGNED TO DATE IN DATE OUT ADMIN DUE DATE: 08/16/99
DIV : HED / / / /
BRAN: IO / / / /
SECT: IO / / / /
REVR : / / / /
CONTR: / / / /
NEGOT DATE: / /
PROJ DATE: / /

* * * DATA REVIEW INSTRUCTIONS * * *

to STEVE WEISS:
Please review Novartis proposed method (pinpunched 6/3/99)
to reduce REI when it is based on eye irritation. Current
protocol results in REI of 48 hours; Novartis says their
method would support 12 hours. If approved, this
methodology could be used for other chemicals as well as
current product (emamectin, #100-904). This is also being
sent to Johnathan Becker (HED) and John Redden (RD/tox). If
questions call Tom Harris, 308-9423, rm 213 CM2. Thanks.

* * * DATA PACKAGE EVALUATION * * *

No evaluation is written for this data package

* * * ADDITIONAL DATA PACKAGES FOR THIS SUBMISSION * * *

| DP BC | BRANCH/SECTION | DATE OUT | DUE BACK | INS | CSF | LABEL |
|--------|----------------|----------|----------|-----|-----|-------|
| 256645 | IO/IO | 06/07/99 | 08/16/99 | Y | Y | Y |

Thomas Harris

02/28/2002 06:00 PM

To: Jack Arthur/DC/USEPA/US@EPA

cc: Stephen Dapson/DC/USEPA/US@EPA, Kathleen
Raffaele/DC/USEPA/US@EPA

Subject: Emamectin Bean - REI

(Steve-FYI, Kathy-FYI last paragraph)

Jack,

ORE

The new bean (D281275) takes care of your ORE work for tolerance 7F4845 (emamectin cotton, etc). It's actually a sub-bean Steve created under one of HED's two main beans for the tolerance.

REI

I was also trying to figure out where we are on the 12-hour REI issue for emamectin. I remember thinking I had tied resolution of Syngenta's request to lower the REI (alot: from 48 to 12 hours) to the tolerance so the work could get scheduled and credited. I think I did that by noting the issue on some of the workplan drafts but the bean(s) are actually under one of the end-use products since that is where the REI text appears. The current open beans are only under 100-903 (I had duplicate beans under the other label 100-904 but it was getting too confusing so I dropped those). Looks like these beans are still open:

100-903

S563354 (352 test protocol; proposed method to reduce REI triggered by eye irritation)
D265288
D256726

Unfortunately, the instructions in PRATS self-destruct when the database gets full so I have no idea what these beans were created for (I can't find a print from when I created them). I would suggest using one or both to resolve any issues regarding the REI. >>> **Are we still on track to resolving the REI issue one way or the other?**

BTW, in case you're not totally confused yet, let me throw in another number. This is actually for avermectin, not emamectin, but I always forget that and wind up trying to track it down every time the emamectin REI issue comes up. Under 100-895 (avermectin technical) bean D265197 is still open for the review of a confirmatory eye irritation study. I think Kathy Raffaele has this; last time I checked it was still out for secondary review. Relevant kind of study, wrong chemical, it has nothing to do with the 12 hour emamectin REI issue. I'll try to remember that and not ask you about it!!!!

Tom Harris
EPA/OPPTS/OPP/RD/IRB
(703) 308-9423
harris.thomas@epa.gov



Thomas Harris
06/20/2000 10:07 AM

To: Jack Arthur/DC/USEPA/US@EPA, Jonathan Becker/DC/USEPA/US@EPA, Kathleen Raffaele/DC/USEPA/US@EPA

cc:

Subject: 12 hr REI protocol: will do w/ 7F4845

Jonathan, Jack, Kathy:

[see note below FYI]

You each have beans from me regarding a Novartis protocol to reduce REI's using dislodgeable foliar residue data. Their specific request is to reduce emamectin from 48 to 12 hrs but the approach might be useful for any chemical as well. [Becker: D256726; Arthur: D265289; Raffaele: D265288]

This work has become more involved than initial expected and really needs to be worked into the OPP workplan so you all have time allocated for this review. To do this, we'll make it part of the upcoming analysis for tolerance petition 7F4845 (emamectin - fruiting veg, leafy veg, leafy Brassica veg, cotton). You haven't seen the beans or data for this tolerance yet but it was granted OP replacement and will be on the FY2001 OPP workplan.

Hope that helps. I know this was getting to be more than we could easily squeeze in so this way it will become part of a plan activity.


-Tom Harris
RD/IRB
308-9423

P.S. - Kathy, this is separate from the avermectin eye irritation study review (D265197) I sent you. That bean is due soon (it's a condition for a product registration). That is a (hopefully) confirmatory study done using technical instead of end-use product to resolve the eye tox category for avermectin. It's so easy to get these two chemicals mixed up!

----- Forwarded by Thomas Harris/DC/USEPA/US on 06/20/2000 09:50 AM



Thomas Harris
06/20/2000 09:50 AM

To: robert.wurz@cp.novartis.com
cc: Tina Levine/DC/USEPA/US@EPA
Subject: 12 hr REI protocol: will do w/ 7F4845 

Robert,

Re: protocol to reduce REI using DFR (specifically emamectin)

I mentioned to you recently that EPA was having difficulty fitting in a review of your

5/20/99 rationale to reduce the re-entry interval for emamectin from 48 to 12 hours. This review was turning out to be more complicated than initially thought and is involving a significant amount of time since it involves a previously submitted study on dislodgeable foliar residues on celery which, unfortunately, had never been reviewed. The amount of time required to review the studies involved and then review the proposed protocol was exceeding our capacity to squeeze in along with regularly scheduled reviews. Therefore, the REI protocol review needs to be officially worked into the OPP workplan.

We've come up with a solution which will hopefully move this along to a timely (ok, that's a relative term) conclusion without formally involving the company priority system. OPP will fold the review of Novartis' proposal to reduce the emamectin REI into the review of tolerance petition 7F4845 (fruiting veg, leafy veg, Leafy Brassica veg, cotton). That tolerance was granted OP replacement status 11/99 and is therefore included in the OPP FY2001 workplan. OPP is currently finalizing that workplan so I don't have any specific target dates yet beyond an FY2001 completion; I'll keep you posted.

-Tom Harris
OPP/RD/IRB
(703) 308-9423



robert.wurz@cp.novartis.com on 03/03/2000 04:52:27 PM

To: Thomas Harris/DC/USEPA/US@EPA
cc:
Subject: RE: Abamectin notes & Enamectin FYI

Hi Tom,

The notes from the Abamectin meeting on proposed E-fate studies were great. No changes at this time.

Follow-up on the emamectin REI discussion we had. Novartis has another product that falls into the same situation with eye irritation/48-hour REI parameters. The product is a fungicide called Ridomil Gold EC. We plan to make a similar argument for Ridomil Gold as we did for Proclaim. As soon as we do I will let you know and you can confab with the Fungicide branch on how to speed HED along.

Have a great weekend.

> Robert Wurz
> Regulatory Affairs
> Novartis Crop Protection, Inc.
> 336 632-2391
> In the ability to dream is the possibility to achieve.
>



robert.wurz@cp.novartis.com on 10/14/99 01:06:37 PM

To: Thomas Harris/DC/USEPA/US@EPA

CC:

Subject: DFR citation

> Tom,
> The citation for the Enamectin dislodgeable study.
>
> MRID 44007903
> Dunbar, D. (1996) Dissipation of Dislodgeable MK-0244 0.16 EC
> Residues from Foliage of Celery when Applied with Non-ionic
> Surfactants by Ground Equipment: Lab Project Number:
> 618-244-93859: 001-93-5010R: 93859. Unpublished study
> prepared
> by Merck Research Labs; Plant Sciences, Inc.; and Agvise Labs.
> 943 p.
>
>
> Robert Wurz
> Regulatory Affairs
> Novartis Crop Protection, Inc.
> 336 632-2391
> In the ability to dream is the possibility to achieve.
>



Jonathan Becker
10/14/99 09:54 AM

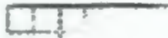
To: Thomas Harris/DC/USEPA/US@EPA
cc:
Subject: Re: status of emamectin protocol review

Tom,

I haven't gotten the topic together enough for a presentation to the Exposure SAC. Based on what I did before, I don't think we could make any decision concerning this specific chemical (versus the general approach of calculating an eye irritation REI) until the DFR study has been reviewed and secondaried and the toxicologist reviews the eye studies to see if they are adequate. Do you know the status of these?

Jonathan

Thomas Harris



Thomas Harris
10/14/99 09:47 AM

To: Jonathan Becker/DC/USEPA/US@EPA
cc:
Subject: Re: status of emamectin protocol review

Jonathan,

When does the Exposure SAC meet? Do you have a target date for when this might be completed? The company is asking me about. Thanks.

-Tom

Jonathan Becker



Jonathan Becker
10/05/99 12:11 PM

To: Thomas Harris/DC/USEPA/US@EPA
cc: Steven Weiss/DC/USEPA/US@EPA
Subject: Re: status of emamectin protocol review

Tom,

I had started working on this shortly after receiving the materials, but to tell you the truth, it was buried on my desk under the press of other tasks. I will dig it out and present it to the Exposure SAC for discussion.

Sorry.

Jonathan

Thomas Harris



Thomas Harris
10/05/99 10:08 AM

To: Steven Weiss/DC/USEPA/US@EPA, Jonathan Becker/DC/USEPA/US@EPA
cc:
Subject: status of emamectin protocol review

RE: EPA reg # 100-904
S563186
D256645 (Jonathan) and D256646 (Steve)

Just checking on the status of a protocol review I sent each of you last May concerning emamectin. The registrant is trying to reduce the re-entry interval based on a sort of "dislodgeable foliar residue" methodology to reduce the REI when based on eye irritation. Do you have a target completion date? Just reply to this note or give me a call. Thanks.

-Tom Harris
RD/IRB
213 CM2
308-9423



5/20/99?

Filed w/ 100-903
100-904

Mr. Thomas Harris
Office of Pesticide Programs H7504C
U.S. Environmental Protection Agency
401 M Street S.W.
Washington, DC 20460

SUBJECT: EMAMECTIN BENZOATE: PP NO. 6F4628;
PROCLAIM™, EPA REG. NO. 100-904,
RATIONALE FOR A 12-HOUR RE-ENTRY INTERVAL (REI)

Dear Mr. Harris,

Novartis has received the 5/10/99 HED denial of our request to reduce the Proclaim REI. Novartis disagrees with the decision, but believes EPA has provided the opportunity to present a reasonable and conservative rationale for reducing the REI while preserving excellent worker safety. The last sentence of the review states that "The Agency welcomes the submission of possible mechanisms for determining REIs based on skin and eye irritation potential".

Novartis presents in this letter the following additional information regarding the appropriate establishment of a 12-hour REI:

- ◆ Using DFR data, primary eye irritation data and conservative assumptions, Novartis has calculated a "Tier 1" assessment for ocular exposure and risk. The assessment demonstrates a large margin of safety for Proclaim even at 0-hours after application.
- ◆ The use of Proclaim will overall increase worker safety when it replaces toxic insecticides, such as organophosphates, that result in much larger exposures and lower margins of safety.
- ◆ Low contact and low exposure characterize re-entry activities that will occur in the field between 12 and 48-hours after application.

Assessment for Ocular Exposure and Risk

To determine a reasonable method to assess ocular safety, we first assumed that the primary route of eye exposure is via the hand. From that point, there are three steps taken to complete an exposure and risk assessment.

- ◆ Calculate the amount of residue transferred from the treated foliage to the hands.
- ◆ Determine a benchmark dose associated with an eye irritation effect that corresponds to a 12-hour REI.
- ◆ Calculate the amount of residue transferred from the hands to the eye. Compare the transferred dose to the benchmark dose to determine a relative margin of safety.

Re-entry Dermal Exposure

In order to assess the hand to eye transfer of residues, the dermal exposure must first be predicted. Applications of Proclaim will result in residues of the active ingredient on the treated leaf surfaces, which then might be available to be dislodged by dermal contact with workers. The amount of active ingredient available to be dislodged was determined in a foliar dislodgeable residue study conducted in 1993 with Denim™ (code name MK-0244 0.16 EC). The study was conducted at Plant Sciences, Inc., in the coastal town of Watsonville, California, adjacent to the Salinas Valley. Two groundboom applications, 7 days apart, were made to celery at 0.015 lb ai/A. Leaf disk samples were collected prior to each application, post-application, and at 1, 3, 7, and 14 days after the second application. The leaf disk residues were dislodged at Plant Sciences, Inc. in an aqueous Triton X-100 solution before being frozen and sent to the Merck Research Laboratories in Rahway, New Jersey for analysis.

Merck
MRID
44007903
1996

Results from the study showed that the dislodgeable residues dissipated to less than the minimum quantifiable limit by 6 days after application. At the average time 0, immediately following application, residues were low, 0.00473 ug/cm² and represented approximately 2 to 3 % of the application rate. A log (natural logarithm)-linear regression curve was generated with an R value of -0.989. The half-life was determined to be 15.6 hours. The dislodgeable residues and half-life are expected to be the same for Proclaim.

The regression curve was used to determine the dislodgeable foliar residue (DFR) at various time points following application; this was then used in the following equation to determine the exposure levels to re-entry workers coming into contact with the treated foliage. A transfer coefficient of 1,000 cm²/hr was used to represent dermal transfer during activities such as scouting and irrigation (HED Risk Assessment, 1999). It is assumed that a re-entry worker would spend 8 hours per day in a field, or in multiple fields, that had been treated with Denim or Proclaim. The ARTF Scope Survey lists the average time spent per day performing various re-entry activities. The activity of

irrigating ranges from an average of 3 hours per day to 7.5 hours per day in lettuce and broccoli; whereas scouting averages only 0.3 to 4 hours per day in broccoli. Based on these survey values, an estimate of working 8 hours per day in a treated field would provide a conservative estimate of exposure.

$$\text{Exposure} = \text{DFR (ug/cm}^2\text{)} \times \text{TC (cm}^2\text{/hr)} \times \text{Time (hr/day)} \times 0.001 \text{ mg/ug} \times (1/70 \text{ kg})$$

$$\text{Exposure (t=0)} = 0.004732 \text{ ug/cm}^2 \times 1,000 \text{ cm}^2\text{/hr} \times 8 \text{ hr} \times 0.001 \text{ mg/ug} \times (1/70 \text{ kg})$$

$$\text{Exposure (t=0)} = 5.4 \times 10^{-4} \text{ mg/kg/day}$$

Exposure was then compared to the NOEL of 22.1 mg ai/kg/day from the 21-day rabbit dermal toxicity study (MRID No. 42743625). This would be the most appropriate toxicological study to use as the primary route of exposure to workers is through the skin. The margin of exposure (MOE) is calculated by dividing the NOEL by the exposure value. An MOE of 100 indicates acceptable risk. The MOEs for various re-entry intervals are listed in Table 1. Even at time 0 (immediately following application), the MOE for anticipated exposure to Proclaim or Denim is around 40,000, which is 400 times the acceptable risk, indicating wide margins of safety.

Table 1: Margins of Exposure for Workers Re-entering Enamectin Benzoate Treated Fields at Various Time Intervals After Application

| Time After Application (Hours) | DFR (ug/cm ²) ¹ | Exposure (mg/kg/day) ¹ | MOE (NOEL/Exposure) |
|--------------------------------|--|-----------------------------------|---------------------|
| 0 | 0.004732 | 5.4 x 10 ⁻⁴ | 40,863 |
| 4 | 0.003962 | 4.5 x 10 ⁻⁴ | 48,811 |
| 8 | 0.003327 | 3.8 x 10 ⁻⁴ | 58,304 |
| 12 | 0.002777 | 3.2 x 10 ⁻⁴ | 69,643 |
| 24 | 0.001629 | 1.9 x 10 ⁻⁴ | 118,694 |
| 48 | 0.000561 | 6.4 x 10 ⁻⁵ | 344,766 |

¹ active ingredient

Ocular Effects Benchmark

In the acute eye irritation experiments, severe eye irritation was observed in rabbits after administration of 100 µl (28 mg) of emamectin benzoate technical (MRID No. 42743615). The changes were not reversible within the observation period of 21 days which put the test material into toxicity category I. A primary acute eye irritation study with 100 µl of the formulated 5 SG product, equivalent to 5 mg of emamectin benzoate, resulted in only slight eye irritation, which was completely reversible within 7 days, and a toxicity category III rating (MRID No. 43824005). (A study was also done using the formulated 0.16 EC product, which also resulted in a ranking of toxicity category I. However the eye irritation is attributed to the hexanol solvent at >50% in the formulation.) The experiments show that the severity of the irritation reaction in the rabbit eye is clearly related to the amount of test material administered. In both tests, the active ingredient was deposited in the conjunctival sac and brought into contact with the cornea of the rabbits in the form of one concentrated droplet. In contrast, the potential for ocular exposure to re-entry workers would occur from repeated smearing with very small amounts of finely dispersed material, which will immediately be diluted by the tear film of the eye. It further has to be kept in mind that the test system in rabbits generally shows a greater sensitivity than the human eye and therefore tends to over-estimate hazard.

Re-entry Eye Exposure

In calculating the ocular exposure assessment, we assume that some of the dislodgeable residues might find their way into the eyes of a re-entry worker and that the most likely route of residue transfer is from hand to eye. Since the model for re-entry exposure does not explicitly establish how much residue would be on each body part, we will conservatively assume that the *entire dermal exposure is concentrated on the hands*. In order to determine how much residue would be on the hands immediately following application, the exposure value at $t=0$ of 5.4×10^{-4} mg/kg/day is multiplied by the default body weight of 70 kg to obtain 0.0378 mg of residue. This total residue is conservatively assumed to be the maximum amount of residue that would accumulate on both the worker's hands following 8 hours of contact with treated plants. If a worker were to transfer *50% of the amount from one hand to one eye*, he would deposit 0.00945 mg of the active ingredient into the eye. This amount is approximately 3 orders of magnitude less than a dose that would result in a slight effect.

The following table presents the potential amount of residue on the hand and the potential amount that could be transferred to the eye along with the corresponding MOE. The MOE is calculated using the 5 mg as an observable effect level that corresponds to slight reversible eye irritation and is associated with a 12-hour REI. The MOE values are calculated using the extreme assumptions above, and also using less extreme but still conservative assumptions (50% dermal residue on hands; 20% transfer from hand to eye).

Table 2: Conservative Model for Potential Amount of Active Ingredient Transferred to the Eye and Corresponding MOE

| Time After Application (Hours) | Hand Residue ¹ (mg) | Amount Transferred to Eye ² (mg) | Worst Case MOE (5 mg/exposure) | Conservative MOE ³ (5 mg/exposure) |
|--------------------------------|--------------------------------|---|--------------------------------|---|
| 0 | 0.03786 | 0.00946 | 528 | 2641 |
| 4 | 0.03169 | 0.00792 | 631 | 3151 |
| 8 | 0.02653 | 0.00663 | 754 | 3769 |
| 12 | 0.02221 | 0.00555 | 900 | 4502 |
| 24 | 0.01303 | 0.00326 | 1535 | 7673 |
| 48 | 0.00449 | 0.00112 | 4457 | 22286 |

¹Assumed 100% of the total bodily residue is located on the hands

²Assumed 50% of the residue on one hand is transferred to the eye

³Calculation based on 50% of the total bodily residue is located on the hands and 20% of the residue on one hand is transferred to the eye

As a comparison, in order to deposit 5 mg of emamectin benzoate, the amount that elicits a slight reversible effect (12-hour RED), into the eye, a worker would have to accumulate 10 mg of residue on his hand. This scenario would be physically and logistically impossible as it would require that *1500% of the applied rate* would have to be dislodged from the plants, or, assuming a 3% dislodgeable residue value (as determined in the DFR study), the worker would have to work for approximately *4500 hours*.

Based on the calculation of transfer from the hand to the eye and the experimental toxicity data outlined above, it is highly unlikely that any eye irritation due to pesticide residues will arise in humans re-entering fields that have been sprayed with Proclaim or Denim.

Opportunity for Worker Risk Reduction via the Use of Proclaim and Denim

The use of Proclaim and Denim has the potential to reduce the risk to mixer/loaders, applicators and field workers when compared to the use of alternative toxic products. Both Proclaim and Denim offer an advantage due to their very low use rates and the very small amounts of dislodgable residue. If Proclaim and Denim are burdened with a 48-hour REI, the use of the product will be reduced greatly. The REI is one of the aspects of a pesticide considered by growers when making purchase and application decisions. A 48-hour REI would put Proclaim and Denim into the same REI category as several organophosphate and carbamate insecticides and worse than most others. When considering which of these products to use, the grower would most likely choose an organophosphate or carbamate for the following reasons:

- Organophosphate and carbamate products are cheaper than emamectin benzoate products.
- Organophosphate and carbamate products are less selective than emamectin benzoate products.

Many of these organophosphate and carbamate products, however, have issues with worker exposure. Several of the organophosphate risk assessments released by EPA to the public have calculated margins of exposure that are unacceptable. In addition, these products are used at active ingredient (ai) rates 45 to 100 times greater than Proclaim and Denim. EPA has calculated the predicted worker exposure risks for both Proclaim and Denim and found wide margins of safety. Therefore, the substitution of these organophosphate and carbamate products with emamectin benzoate products would improve worker safety.

Proclaim and Denim with 12-hour REI's are projected to replace a substantial amount of the use of certain organophosphate and carbamate products. Table 3 demonstrates the numbers of acres projected to be treated with Proclaim and Denim at the expense of less safe products. In total, worker safety could be improved on at least 812,379 acres per year in the US. In fact, this enhancement of worker and food safety has convinced Novartis to submit a Reduced Risk rationale for the next emamectin benzoate petition.

Table 3. Replacement Potential of Proclaim and Denim with 12-hour REI for Current and Proposed Uses

| Product | Max. Single App. Rate (lbs ai/A) | Acres Treated with Product | Signal Word and REI (hours) | % Load Reduction on a Per Acre Basis | Projected Emamectin benzoate Acre Share % | Total Projected Reduction in Acres Treated with Alternative |
|---|----------------------------------|----------------------------|-----------------------------|--------------------------------------|---|---|
| Use Patterns for Insecticides Targeting Lepidopteran Species in Cole Crop in the U.S. during 1998. | | | | | | |
| Endosulfan (Thiodan) | 1 | 5400 | Danger-Poison, 24 | 99% | 20% | 1080 |
| Methomyl (Lannate) | 0.9 | 56,060 | Danger-Poison, 48 | 98 % | 25% | 14,015 |
| Chlorpyrifos (Lorsban) | 1 | 34,397 | Warning, 24 | 99 % | 25% | 8599 |
| Use Patterns for Insecticides Targeting Lepidopteran Species in Leafy Vegetables in the U.S. (1998) | | | | | | |
| Endosulfan | 1 | 12,912 | Danger-Poison, 24 | 99% | 20% | 2582 |
| Methomyl | 0.9 | 428,735 | Danger-Poison, 48 | 98 % | 20% | 85,747 |
| Acephate (Orthene) | 1 | 114,543 | Caution, 24 | 99 % | 20% | 22,909 |
| Thiodicarb (Larvin) | 0.75 | 90,836 | Warning, 12 | 98 % | 10% | 9084 |
| Use Patterns for Insecticides Targeting Lepidopteran Species in Fruiting Vegetables in the U.S. (1998) | | | | | | |
| Endosulfan | 1 | 22,700 | Danger-Poison, 24 | 99% | 20% | 4540 |
| Methamidophos (Monitor) | 1 | 7,000 | Danger-Poison, 48 | 99% | 20% | 1400 |
| Methomyl | 0.9 | 309,476 | Danger-Poison, 48 | 98 % | 20% | 61895 |
| Use Patterns for Insecticides Targeting Lepidopteran Species in Cotton in the U.S. during 1998 | | | | | | |
| Profenofos (Curacron) | 1 | 425,592 | Warning 48 | 99 % | 20% | 85,118 |
| Methomyl | 0.45 | 278,172 | Danger-Poison, 48 | 98 % | 25% | 69,543 |
| Chlorpyrifos | 1 | 275,014 | Warning, 24 | 99 % | 30% | 82,504 |
| Thiodicarb | 0.9 | 249,922 | Warning, 12 | 99 % | 30% | 74,977 |
| Acephate | 1 | 207,605 | Caution, 24 | 99 % | 10% | 20,761 |
| Use Patterns for Insecticides Targeting Lepidopteran Species in Tobacco in the U.S. during 1998. | | | | | | |
| Endosulfan | 1 | 82,827 | Danger-Poison, 24 | 99% | 20% | 16,565 |
| Acephate | 0.75 | 900,037 | Caution, 24 | 99 % | 25 % | 225,009 |
| Methomyl | 0.45 | 130,257 | Danger-Poison, 48 | 98 % | 20 % | 26051 |
| | | | | | | Total 812,379 |

Re-entry Activities for Proclaim and Denim are Low Exposure

Low contact and low exposure characterize the activities that will occur in the field between 12 and 48-hours after application. The pre-harvest interval (PHI) for Proclaim 5 SG and Denim is 7 days. Therefore, harvesting activities will not take place immediately following application. Only low exposure activities such as thinning, weeding, moving irrigation pipes, and applying fertilizers or pesticides would occur in the time between 12 and 48-hours after application.

The ARTF (Agricultural Re-entry Task Force) conducted a large-scale survey of growers throughout the United States and Canada regarding what types of re-entry activities exist and the potential for bodily contact with the crop. The development, implementation, and evaluation of the survey were done with input from technical representatives from the U.S. EPA, CDPR, and Health Canada. The completed survey was submitted to EPA in March of 1999, and has the MRID number 44802601. The data collected in this survey was evaluated and grouped into clusters which contain various crop-activity combinations that resulted in similar contact with four major body parts (legs, hands, forearms, and upper body). The higher the cluster number, the smaller the contact with the crop. The cluster numbers range from 1 to 28.

Activities that must occur soon after an insecticide application are thinning, hand-weeding, and irrigation; these tasks fall into clusters 26, 26, and 28/23 for broccoli and clusters 26, 22/26, and 22 for lettuce, respectively. The higher cluster number indicates relatively less proportion of contact for each body part with the treated plant. For instance, in setting up irrigation systems in mature lettuce fields, it is estimated that percent of the hand in contact with foliage is 67% while upper body contact is 20%. Although these numbers are subjective measurements, they do give an idea of relative contact with the crop. Based on the cluster these activities fall into, it is apparent that these are not high contact activities.

In conclusion, Novartis has justified the establishment of a 12-hour REI for Proclaim by the following reasons.

- ◆ Novartis has demonstrated a reasonable and conservative method to assess ocular risk due to re-entry activities.
- ◆ Proclaim has wide margins of safety with respect to re-entry ocular exposure and risk immediately following application.
- ◆ The increased use of Proclaim due to a 12-hour REI will displace other products that have worker exposure issues.
- ◆ The activities performed between 12 and 48 hours after application are low contact and result in low exposure.

Novartis respectfully requests that the Agency approves, with all due haste, a Proclaim label amendment for a 12-hour REI. If you have any questions or comments, please contact me at (336) 632-2391.

Sincerely,



Robert E. M. Wurz, Ph.D.
Senior Regulatory Manager
Regulatory Affairs

cc: Mr. Arnold Layne
Ms. Tina Levine



May 13, 1999

Mr. Thomas Harris
Office of Pesticide Programs H7504C
U.S. Environmental Protection Agency
401 M Street S.W.
Washington, DC 20460

SUBJECT: EMAMECTIN BENZOATE: PP NO. 6F4628;
PROCLAIM™, EPA REG. NO. 100-904,
REQUEST FOR A MEETING TO DISCUSS THE RATIONALE FOR A
12-HOUR RE-ENTRY INTERVAL (REI)

Dear Mr. Harris,

Novartis has received the 5/10/99 HED review of our request to reduce the Proclaim REI. While Novartis is disappointed with the outcome, we believe EPA has provided the opportunity to present a reasonable and conservative rationale for reducing the REI while preserving excellent worker safety. The EPA states in the last sentence of the review that "The Agency welcomes the submission of possible mechanisms for determining REIs based on skin and eye irritation potential".

Novartis requests a meeting with EPA to present and discuss the following additional information regarding the REI:

- Using DFR data, primary eye irritation data and conservative assumptions, Novartis has calculated a "Tier 1" assessment for ocular exposure and risk. The assessment demonstrates a large margin of safety for Proclaim even at 0-hours after application.
- The use of Proclaim will overall increase worker safety when it replaces toxic insecticides, such as organophosphates, that result in much larger exposures.

In order to expedite this process, Novartis would be delighted to meet with the Agency on any of the following dates: May 19, 20, and 21. Novartis requests the attendance of Steven Weiss, Richard Loranger, Tom Harris, Arnold Layne in addition to other persons that the Agency believes are instrumental to achieving a reasonable and timely resolution of this issue.

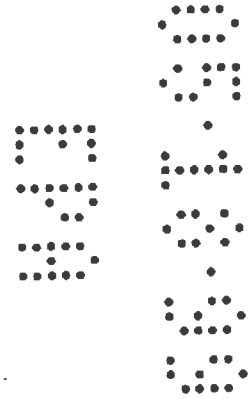
If you have any questions or comments, please contact me at (336) 632-2391.

Sincerely,



Robert E. M. Wurz, Ph.D.
Senior Regulatory Manager
Regulatory Affairs

cc: Mr. George LaRocca
Mr. Arnold Layne





robert.wurz@cp.novartis.com on 05/12/99 04:50:12 PM

To: Thomas Harris/DC/USEPA/US@EPA
cc:
Subject: Proclaim REI

Tom,
FYI, in case you had not received the Proclaim REI review. Novartis has an internal meeting tomorrow morning. We will work out a response and meeting request with some "meat" in it and FAX it to you in the afternoon.
Regards,
Robert

-----Original Message-----

From: LaRocca.George@epamail.epa.gov
[mailto:LaRocca.George@epamail.epa.gov]
Sent: Wednesday, May 12, 1999 12:30 PM
To: Wurz Robert CP USGR EXC
Subject: Re: E-mail address

Here is our response to your March 16, 1999 rationale for a 12 - hour re-entry interval. In responding you should also be more specific in identifying what hand tasks are sensitive to a 48 hr REI. We don't believe any of the tasks you have identified are time sensitive or not already allowed under the WPS program regardless of the REI.

George LaRocca

John Leahy
05/11/99 02:45 PM

To: George Larocca@EPA
cc:
Subject: REI memo

Here's the memo

----- Forwarded by John Leahy/DC/USEPA/US on 05/11/99 02:53 PM -----


Steven Weiss
05/11/99 02:37 PM

To: John Leahy/DC/USEPA/US@EPA
cc:
Subject: REI memo

(See attached file: D254469.mem)



- D254469.mem

 _____
To: Thomas Harris/DC/USEPA/US@EPA
CC:
Subject: Re: HEADS UP/Emamectin benzoate REI Issue

fyi


----- Forwarded by George LaRocca/DC/USEPA/US on 05/05/99 03:23 PM -----

 _____
To: Donna Davis/DC/USEPA/US@EPA
cc: Steven Weiss/DC/USEPA/US@EPA
Subject: Re: HEADS UP/Emamectin benzoate REI Issue 

Donna - Arnold Layne will be contacting you to further discuss this issue. I did speak with John Leahy (who is on leave until next week) after he spoke with Steve and got the scoop on this. I thought after talking to John that Steve was finishing a draft response to Novartis March 16th rebuttal. If the answer is no I think we have to explain why rather than just say it is "WPS policy" especially in light of their referencing post application exposure and crop dislodgeable residue data. Novartis is ready to come in now with additional info if necessary to support this change. I will talk to John when he gets back about entertaining a meeting with Novartis but I am not sure he will want to do it alone. The other wrinkle is this chemical passes on to Tina's Branch after registration so our team will eventually be out of the loop.

George LaRocca
Donna Davis

 Donna Davis
05/03/99 04:34 PM

To: George LaRocca/DC/USEPA/US@EPA
cc: Arnold Layne/DC/USEPA/US@EPA, Linda Arrington/DC/USEPA/US@EPA, Steven Weiss/DC/USEPA/US@EPA
Subject: Re: HEADS UP/Emamectin benzoate REI Issue 


George,

The 48 hr REI is a matter of WPS policy. Steve has looked at the rebuttal for both emamectin and avermectin and concludes that it does nothing to change the existing WPS policy. Steve has other more pressing work right now and since the company has not provided anything significant that would change the ruling, that is a lower priority.

I was under the impression that Steve had spoken with John Leahy and that John would attend a meeting if the registrant needed one. The issue is bigger than these two chemicals, it would be a matter of changing WPS policy - that is not going to be resolved by a single ORE reviewer.

Donna

George LaRocca

 _____
To: Arnold Layne/DC/USEPA/US
cc: Donna Davis/DC/USEPA/US@EPA, Linda Arrington/DC/USEPA/US@EPA
Subject: HEADS UP/Emamectin benzoate REI Issue

Arnold - I spoke to Dick Fulner of Novartis today who intends to call you next week to schedule a meeting

with us(Jim, if available) and HED to discuss retention of the 12-hour REI for use of emamectin on head and stem brassica, lettuce and celery. HED calls for a 48 REI to comply with the WPS. This is based on a Tox Cat 1 classification for primary eye irritation.

Novartis was looking to meet either on the 6th, 12th, or 13th of May. Novartis claims that a 48 REI would be a significant hindrance to use the product and that they could not get it registered in the States with such a restriction. They submitted their rationale for 12 hr REI on March 16th, 1999. It is currently in HED and I believe a response(negative) is being prepared now(Donna- Is that correct?)

I told Dick that it would not be appropriate to schedule a meeting until HED completed their review and Novartis had the opportunity to assess our arguments after which we would determine the need for a meeting. I indicated that for purposes of registration of Emamectin next week they would have to place the 48 REI on their labeling. They agreed to make the label change for registration purposes but were going to aggressively pursue the change.

George LaRocca



robert.wurz@cp.novartis.com on 05/04/99 05:24:04 PM

To: Tina Levine/DC/USEPA/US@EPA, Thomas Harris/DC/USEPA/US@EPA
cc: dick.feulner@cp.novartis.com
Subject: Emamectin benzoate/Proclaim REI!

Tina & Tom,

I just talked with George LaRocca about the emamectin benzoate REI issue, and he indicated that you two would really be handling this issue since registration is imminent. I wanted to reinforce that the 48-hour REI is a serious issue for the product. I ask for your support in moving HED to finish any comments they have for us and scheduling a meeting to discuss the REI. In this effort, We've received verbal affirmations of support from Jim Jones and Arnold Layne.

We have done some preliminary work based on the sketchy information we have concerning HED objections to our proposed REI. We've discovered that the product is safer for reentry than we thought.
For example:

- * Re-entry activities associated with Proclaim are low-contact activities based on ARTF scope survey results
 - * Calculations of amount of active ingredient transferred to eye showed it to be 1000X less than a dose that causes only a mild, reversible effect (tox category III).
 - * Data from the DFR study support a 4-hour REI.
- I hope we can quickly resolve this issue with your help.

Regards,
Robert Wurz
Novartis Crop Protection
336 632-2391

- who is responsible at EPA
- how to proceed



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APR 19 2002

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

John Hott
Syngenta Crop Protection, Inc.
PO Box 18300
Greensboro, NC 27419

re: Enamectin Benzoate Technical, EPA Reg. # 100-902
conditional registration extended until 5/1/03

Dear Mr. Hott:

The above product was conditionally registered on 5/19/99 with an expiration date of 5/1/02. This letter serves to extend the conditional registration expiration date for this product for one year, i.e. until 5/1/03. This will allow additional time for execution, submission, and review of the estuarine/marine invertebrate life-cycle study (guideline OPP 72-4b = OPPTS 850.1350) which is noted as a requirement on the Notice of Registration for EPA Registration numbers 100-903 and 100-904. A request to waive this requirement was denied by EPA on 6/1/01. The study must be submitted to EPA sufficiently in advance of the registration expiration date to allow EPA to review the study and determine if it is acceptable. Once this remaining data gap is filled EPA may issue an unconditional registration for all three products.

If you have any questions please contact me at (703) 308-9423 or
harris.thomas@epa.gov.

Yours truly,

TS

Thomas C. Harris, Biologist
Insecticide-Rodenticide Branch
Registration Division (7505C)

Page 1 of 1

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john.hott@syngenta.com

04/12/2002 09:53
AM

To: Thomas Harris/DC/USEPA/US@EPA
cc:
Subject: Emamectin mysid study

Tom,

We would appreciate an extension on the emamectin mysid study "to be submitted" by August 1st, 2002. Thank you for your help! And, please let me know if this timeframe is OK.

John

John L. Hott, Ph.D.
Regulatory Product Manager
Syngenta Crop Protection, Inc.
Regulatory Affairs
P.O. Box 18300
Greensboro, NC 27419-8300
336.632.7096 Office
336.292.6374 FAX
john.hott@syngenta.com



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

April 16, 2002

John Hott
Syngenta Crop Protection, Inc.
PO Box 18300
Greensboro, NC 27419-8300

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

re: sample preparation (washing) for market basket surveys

Dear Mr. Hott:

During a recent conversation you mentioned that Syngenta was planning another market basket survey. Having heard rumors that OPP may have some concerns with the sample preparation procedures in the recent avermectin market basket survey I decided to look into the question. My goal is to resolve any procedural issues before you conduct the next market basket survey and thus head off any potential problems.

The issue concerns washing the commodity during sample preparation. Your procedures for the avermectin market basket survey included the following directions (for apples, in this case) which you stated were taken from the organophosphate market basket survey:

"Wash the apple under medium-flow cold water for approximately 15-20 seconds, rubbing gently. Allow the apple to drain for at least 2 minutes on paper towels on a flat surface."

Close, but not quite correct. Our Health Effects Division has advised me that sample preparation should follow the PDP protocol which states:

"Wash each apple under cold running tap water for approximately 15-20 seconds to assure that all surfaces of the apple have been rinsed. Allow to drain for at least 2 minutes on paper towels on a flat surface."

The main difference is that the PDP protocol specifies that most commodities should NOT be rubbed or scrubbed. There are a very few exceptions (carrots, potatoes, sweet potatoes) where "gently scrub" under cold running tap water is specified. The PDP protocols are available on the internet at:

www.ams.usda.gov/science/pdp/sops.htm main page
www.ams.usda.gov/science/pdp/labop03.pdf sample preparation

For future market basket surveys we request that you follow the PDP guidance cited above.

If you have any questions or comments please contact me at (703) 308-9423 or harris.thomas@epa.gov.

Yours truly,

Thomas C. Harris, Biologist
Insecticide-Rodenticide Branch
Registration Division (7505C)



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D C 20460

JAN 28 2002

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

John Hott
Syngenta Crop Protection, Inc.
PO Box 18300
Greensboro, NC 27419

*COPY
file in
100-402*

re: Enamectin Benzoate, pc code 122806
Analytical Chemistry Methods (MRID # 428689-04, 438501-25) for vegetables
(including leafy vegetables and cole crops) (tolerance petition 6F4628)
acceptable, samples of degradates required

*original
in this
file*

Dear Mr. Hott:

Enclosed please find a copy of the following EPA documents regarding a tolerance method validation of a proposed enforcement method for residues of emamectin on broccoli, et al submitted in conjunction with tolerance 6F4628:

- 1) PP#6F4628. Enamectin Benzoate on Broccoli, Brussels Sprouts, Cabbage, Cauliflower, Lettuce, and Celery. Tolerance Method Validation Prereview of the Proposed Residue Analytical Method ... (MRID 428689-04). 1/27/99.
- 2) PP#6F4628. Enamectin Benzoate on Broccoli, Brussels Sprouts, Cabbage, Cauliflower, Lettuce, and Celery. Tolerance Method Validation Request. (MRID 428689-04, 438501-25). 6/15/99.

Please note the following:

- The 6/15/99 review states that EPA received but did not validate a method using LC/MS (MRID 445963-01). EPA comments are included in the review and the registrant is encouraged to further develop and submit for validation a LC/MS method that would quantitate all five analytes without the need for derivatization.
- The registrant is reminded that they must submit a 5 gram sample of each of the four degradates used in the tolerance expression to the EPA National Repository as per Guideline 830.1900. Also, please see note 5(B) in the 6/15/99 review concerning nomenclature. *These samples are in addition to the sample of the*

Page 1 of 2

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technical grade emamectin benzoate required in EPA's letter dated 9/13/2001 accepting the recent change in formulation for your technical grade emamectin benzoate product (EPA Reg. # 100-902). The samples should be sent to:

Mr. Francis Griffith
EPA/OPP
Analytical Chemistry Laboratory
701 Mapes Road
Fort Mead, Maryland 20755-5350

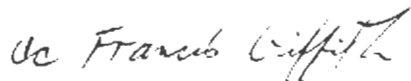
If you have any questions please contact me at (703) 308-9423 or harris.thomas@epa.gov.

Yours truly,



Thomas C. Harris, Biologist
Insecticide-Rodenticide Branch
Registration Division (7505C)

enclosures (2)





UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Analytical Chemistry Branch
701 Mapes Road
Fort Meade, Maryland 20755-5350

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP#6F4628. Enamectin Benzoate on Broccoli, Brussels Sprouts, Cabbage, Cauliflower, Lettuce, and Celery.
Tolerance Method Validation Request.
(MRID#:42868904, 43850125)(Barcode#:D250694) B99-(20-21).

FROM: Elizabeth J. Kolbe, Chemist *EJK*
Douglas Swineford, Chemist *DS*
Analytical Chemistry Branch

THRU: Francis D. Griffith, Jr., Chief *Francis D. Griffith Jr.*
Analytical Chemistry Branch

THRU: Donald A. Marlow, Laboratory Coordinator
Biological and Economic Analysis Division (7503C)

TO: Donna Davis, Chief
Registration Action Branch II
Health Effects Division (7509C)

INTRODUCTION

The Analytical Chemistry Branch (ACB) was requested by the Registration Action Branch II (RAB II) to conduct a tolerance method validation of the proposed enforcement method submitted by Novartis Crop Protection, Inc. for the determination of residues of the insecticide emamectin benzoate in/on broccoli. Novartis Crop Protection, Inc. has requested a permanent tolerance of 0.025 ppm, expressed as the combined residues of emamectin, 8,9 ZMA, and the metabolites/photodegradates (AB1A, MFB1A, and FAB1A, also known as, respectively, L'649, L'599, L'831). This represents the combined limits of quantitation (LOQ) of the proposed method. ACB was requested to fortify broccoli in duplicate at 0.005 ppm, and 0.01 ppm with each component of the tolerance expression.

RECOMMENDATION

1) The method has been successfully validated by ACB. ACB finds the method is suitable for food tolerance enforcement. ACB recommends that this residue analytical method be made available to Federal and State enforcement laboratories along with our addendum, and that the changes made in the EPA addendum be incorporated into the method prior to its use.

2) ACB recommends that this method be forwarded to FDA for publication in PAM II along with our addendum.

METHOD SUMMARY

The submitted method is entitled "Method Validation: HPLC-Fluorescence Method to Determine the Total Toxic Residue of MK-0244 and Its Metabolites on Vegetables, Including Leafy Vegetables and Cole Crops," by T.A. Wehner, dated 6/3/93, and coded **MRID #42868904**.

Refer to memorandum dated January 27, 1999, from M. Law and E. Kolbe, all comments and conclusions are incorporated herein by reference.

INDEPENDENT LABORATORY VALIDATION

ACB has reviewed the ILV report and supporting data. Refer to memorandum dated January 27, 1999, from M. Law and E. Kolbe, all comments and conclusions are incorporated herein by reference.

The recovery data for L'649 and L'831 were low as reported by the petitioner and ACB, the ILV data shows higher recoveries for L'831.

CONCLUSIONS

- 1) ACB concludes that this method minimally meets the requirements for an enforcement method as defined in the Pesticide Test Guideline 860.1340, after our comments, presented in our Addendum, are attached to the petitioner's method.
- 2) The method states a limit of quantitation (LOQ) of 0.005 ppm and a limit of detection (LOD) of 0.001 ppm for each component of the tolerance expression. ACB concurs with the petitioner on the LOQ and LOD.
- 3) A set of six samples can be processed by one analyst in approximately 2 days plus 15 minutes for each instrumental analysis.
- 4) ACB has reviewed but not validated the petitioner's method for emamectin benzoate using LC/MS, "Validation of Analytical Method AG-684 for the Confirmation of Emamectin Benzoate (MK-0244) and its Isomer, 8,9-Z, in or on Representative Samples of Crop Group 4: Leafy Vegetables and Crop

Group 5: Brassica (Cole) Leafy Vegetables by LC/MS", by J.W. James, W.E. Pruitt and K.D. Ediger, dated 6/25/98, and coded MRID # 44596301.

- A) The LC/MS method does not allow for quantitation of L'649 or the metabolites found in the neutral fraction, even though these are included in the tolerance expression.
 - B) This method does eliminate the need to derivatize, which is a troublesome step in the LC/Fluorescence method.
 - C) ACB would encourage the further development of a LC/MS method that would quantitate all five analytes without the need for derivatization. This can be submitted by the petitioner in a later amendment.
- 5) The primary standards were obtained from Novartis. The purity of the standards were greater than 90% except for FAB1A (L'831) which had a purity greater than 79%. The derivatized standards are made by the analyst at the same time the samples are derivatized, just prior to instrument analysis.
- A) The petitioner needs to be reminded that standards for the four degradates should be supplied to the EPA National Repository now located at ACB at the Environmental Science Center.
 - B) The nomenclature used by the petitioner in the analytical method and the one used for labeling the standards needs to be made consistent to prevent confusion.
- 6) The commodity used for the validation was purchased at a local grocery store.

Attachments: Detector Response
EPA Addendum
Method Validation Results

cc:TMV file (B99-(20-21)), ACB Analyst: Kolbe/Swineford
ACB: 7503C: ESC : Kolbe:6/11/99 : (410)305-2959:Swineford : 6/11/99
RDI:QAPanel:6/14/99: MLaw: 6/14/99: BrCh:F.D.Griffith:6/15/99

Emamectin Benzoate and Metabolites in Broccoli

Method Validation: HPLC-Fluorescence Method to Determine the Total Toxic Residue
of MK-0244 and Its Metabolites on Vegetables, Including Leafy Vegetables and Cole Crops".

by T.A. Wehner

PP#6F4628, MRID#4286904, 43850125

| Analyte | ppm Added | ppm Found | % Recovery |
|--------------------|-----------|-----------|------------|
| Emamectin Benzoate | 0.00 | < 0.001 | |
| | 0.00 | < 0.001 | |
| | 0.00488 | 0.00368 | 75 |
| | 0.00488 | 0.00409 | 84 |
| | 0.00976 | 0.00903 | 93 |
| | 0.00976 | 0.00829 | 85 |
| | | | |
| | | | |
| 8,9-ZMA | 0.00 | < 0.001 | |
| | 0.00 | < 0.001 | |
| | 0.00473 | 0.00481 | 102 |
| | 0.00473 | 0.00520 | 110 |
| | 0.00947 | 0.00995 | 105 |
| | 0.00947 | 0.00973 | 103 |
| | | | |
| | | | |
| L'649 (AB1A) | 0.00 | < 0.001 | |
| | 0.00 | < 0.001 | |
| | 0.00460 | 0.00235 | 51 |
| | 0.00460 | 0.00260 | 56 |
| | 0.00919 | 0.00534 | 58 |
| | 0.00919 | 0.00498 | 54 |
| | | | |
| | | | |
| L'599 (MFB1A) | 0.00 | < 0.001 | |
| | 0.00 | < 0.001 | |
| | 0.00474 | 0.00281 | 59 |
| | 0.00474 | 0.00261 | 55 |
| | 0.00947 | 0.00648 | 68 |
| | 0.00947 | 0.00674 | 71 |
| | | | |
| | | | |
| L'831 (FAB1A) | 0.00 | < 0.001 | |
| | 0.00 | < 0.001 | |
| | 0.00496 | 0.00304 | 61 |
| | 0.00496 | 0.00355 | 71 |
| | 0.00992 | 0.00642 | 65 |
| | 0.00992 | 0.00544 | 55 |
| | | | |
| | | | |

Cauliflower, Lettuce, and Celery.

"Method Validation: HPLC-Fluorescence Method to Determine the Total Toxic Residue of MK-0244 and Its Metabolites on Vegetables, Including Leafy Vegetables and Cole Crops," by T.A. Wehner, dated 6/3/93.

EPA ADDENDUM

1) ACB substituted equivalent equipment and materials.

A) ACB used an IKA Works T25 for the high speed homogenizer to extract samples with good results.

B) The commodities were homogenized in a RobtCoupe R 301 Ultra without dry ice.

C) In place of the Kryorack ice water bath for chilling the sample extracts before derivatizing, ACB placed the samples extracts in a freezer for 5 minutes.

2) ACB used a Hewlett Packard (HP) 1050 LC with a HP 1046A Fluorescence detector.

Column: Supelcosil LC-18, 15 cm x 4.6 mm, 3um.

Mobile Phase: 6% water in methanol

Elution: isocratic, run time 15 min.

Flow Rate: 1 ml/min

Injection volume: 50 ul

Xenon lamp: Excitation 365 nm, Emission 470 nm, Cut-off filter 450 nm

PMT gain: 18, Lamp 220 hz, Response time: 1000 msec

3) Users of the method as written need to incorporate these suggestions.

A) ACB and the petitioner's laboratory used 50 ul injection volume, and the ILV laboratory used 100 ul. The method needs to state in the section D. 'HPLC Apparatus and Chromatographic Conditions', the acceptable range of injection volume.

B) The 1-Methylimidazole (NMIM) and trifluoroacetic anhydride (TFAA) were kept in a desiccator in the refrigerator for storage by ACB. They were removed from the refrigerator and allowed to warm to room temperature in the desiccator to prevent moisture from condensing on the interior walls when the bottles were opened.

- C) ACB found that in the ionizable fraction of ethyl acetate (step 24) often minute amounts of water became apparent when concentrated to 1 ml. Care needs to be taken to remove this water, ACB did this by reextracting with 1 or 2 ml ethyl acetate, centrifuging and transferring the ethyl acetate to a fresh tube for concentration to 1 ml. again.
- D) ACB found that even the smallest amount of water or methanol will prevent the derivatization reaction and extreme care should be used to eliminate the presence of these solvents. ACB found that the reaction could fail even when white vapor was formed with the addition of TFAA solution.

Final

Analytical Chemistry Branch
Building 306, BARC-East
Beltsville, Maryland 20705

MEMORANDUM

SUBJECT: PP#6F4628. Emamectin Benzoate on Broccoli, Brussels Sprouts, Cabbage, Cauliflower, Lettuce, and Celery. **Tolerance Method Validation Prereview of the Proposed Residue Analytical Method.** PC Code 287173 (MRID#:42868904)(Barcode#:D250694) B99-(20-21).

FROM: Mark W. Law, Team Leader
Elizabeth J. Kolbe, Chemist
Analytical Chemistry Branch

THRU: Francis D. Griffith, Jr., Chief
Analytical Chemistry Branch

THRU: Donald A. Marlow, Laboratory Coordinator
Biological and Economic Analysis Division (7503C)

TO: Elizabeth Doyle, Chief
Chemical Exposure Branch - I
Health Effects Division (7509C)

And

Mark Dow, Acting Chief
Insecticide Branch
Registration Division (7505C)

INTRODUCTION

The Analytical Chemistry Branch (ACB) was requested by the Registration Division to conduct a tolerance method validation prereview for the insecticide Emamectin Benzoate in/on broccoli. Norvartis Crop Protection, Inc. has requested a permanent tolerance of 0.025 ppm, expressed as the combined residues of emamectin, 8,9 ZMA, and the metabolites/photodegrades (AB1A, MFB1A, and FAB1A). This represents the combined limits of quantitation (LOQ) of the proposed method.

RECOMMENDATION

1. Since this method has not been validated in our laboratory, ACB advises that the method appears suitable for time limited tolerance enforcement only. It should only be distributed to the States granted the Emergency Exemption (Section 18) registration and FDA. ACB has no objection to RD granting an Emergency Exemption Registration (Section 18) with a time limited tolerance and use of this residue analytical method to enforce the time limited tolerance prior to validation in our laboratory.

However, before a permanent tolerance is issued at a future date, ACB should validate the method that supports the tolerance.

2. ACB recommends that the state(s) which is granted the Section 18 registration be encourage to provide RD a copy of all method validation data generated during the time limited tolerance.

METHOD SUMMARY

The submitted method is entitled "Method Validation: HPLC-Fluorescence Method to Determine the Total Toxic Residue of MK-0244 and Its Metabolites on Vegetables, Including Leafy Vegetables and Cole Crops," by T.A. Wehner, dated 6/3/93, and coded **MRID #42868904**.

Sample aliquots of 10 grams are extracted with 15 ml of ethyl acetate, water, and acetonitrile (10:4:1) using a high speed blender. After centrifuging to remove solids, the extract is fractionated on a propylsulfonyl (PRS) cation exchange column and the ionizable compounds (MK-0244, 8,9-Z isomer, and the AB1A metabolite) are separated from the neutral compounds (FAB1A and MFB1A metabolites). The ionizable fraction is eluted from the PRS column with 1% ammonium acetate in methanol and derivatized with trifluoroacetic anhydride. The neutral fraction is eluted from the PRS column with ethyl acetate, and cleaned up by an aminopropyl solid phase cartridge column. The organic solvents are evaporated and the sample is reconstituted in acetonitrile and derivatized with trifluoroacetic anhydride.

The fractions are analyzed separately using a reverse phase column on a HPLC equipped with a fluorescence detector, with an excitation wavelength of 365 nm and emissions measured at 470 nm. The individual residues are then totaled to determine if the tolerance level is exceeded.

The petitioner submitted copies of chromatograms showing a standard, untreated control and fortified sample of broccoli. The petitioner's method validation data showed samples of broccoli spiked at 0.005 - 0.120 ppm MK-0244 B1a had recoveries ranging from 60% to 89%; spiked at 0.005 MK-0244 B1b had recoveries ranging from 61% to 98%; spiked at 0.005 - 0.052 ppm 8,9 Z had recoveries ranging from 54% to 58%; spiked at 0.005 - 0.120 ppm AB1A had recoveries ranging from 41%

to 75%; spiked at 0.005 ppm MFB1A had recoveries of 55% and 57%; spiked at 0.010 - 0.24 ppm MFB1A and FAB1A combined had recoveries ranging from 47% to 59%. These data are acceptable to show the method is minimally suitable to gather magnitude of the residue crop field trial residue data. Based on these data ACB estimated the method's LOQ is 0.025 ppm for the summation of Emamectin Benzoate and its photodegrades.

The Independent Laboratory Validation (ILV) data were generated by EN-CAS Analytical Labs at Winston-Salem, NC. Their report is titled "Independent Method Validation Ruggedness Trial for the Determination of Emamectin Benzoate (MK-0244) and Its Photodegrades on Vegetables using Merck Method No. 244-92-3, Revision 1" by B. G. Baldi, dated 7/26/95 completion, and coded as MRID #43850125.

The ILV laboratory successfully completed their validation of the method on their first attempt. There were no problems reported with the method as written. There were no changes or modifications made by the ILV lab. The method uses widely acceptable equipment reagents and procedures. Samples of broccoli were spiked in duplicate at 0.010 ppm and 0.10 ppm with MK-0244 plus 8,9 Z; AB1A; and MFB1A plus FAB1A. Respective recoveries at 63%, 73% and 69%, 75%; 51%, 69% and 63%, 73%; and 75%, 65% and 79%, 117%. The ILV data included multiple chromatograms of standards, untreated controls and recovery data from fortified samples of broccoli. The ILV data and supporting chromatograms submitted validate the method at its stated LOQ. ACB concludes there has been a successful ILV.

Review of all chromatograms shows minimum interferences at the elution time of the emamectin and its metabolites. They support a limit of quantitation at 0.025 ppm as suggested by the petitioner. There appears to be some slight retention time shifts dependent on the amount present, ACB does not expect this to effect the results of the method.

CONCLUSIONS

1. ACB concludes that the method can be used to enforce a time limited tolerance prior to ACB validating the method. Method users must generate their own data to verify the method prior to use. ACB concludes that the method is written in a stepwise fashion with sufficient detail so that a competent chemist can apply the method as written even though they are unfamiliar with the procedure.
2. Judgement is deferred on the method being suitable to enforce permanent tolerance(s) until there has been a successful TMV. ACB will proceed with a tolerance method validation for this pesticide, but is faced with a potential delay in the completion of this trial due to the move of the laboratory to the new Environmental Science Center.

3. Based on the petitioner's data, ACB estimates the LOQ is 0.025 ppm when all components are summed. We defer judgement on the LOD until completion of the TMV.
4. ACB has reviewed the ILV report and supporting data. The ILV laboratory successfully completed their validation of the method on their first attempt and reported no problems with the method as written. The method uses widely acceptable equipment reagents and procedures. The data and chromatograms submitted by the ILV laboratory validate the method at its stated LOQ.
5. No multiresidue method (MRM) validation data were presented to ACB for review. Absence of such data is a potential deficiency.
6. ACB estimates the time to complete a set of six samples is 2 days plus overnight instrumental analysis based on the method submitted by the petitioner. This may be revised after ACB validates the method.

cc:TMV file B99-20, Reviewers(EJKolbe,MWLaw),Circu.
ACB:7503C:BARC-E,Bldg.306,MWLaw:12/22/98:(301)504-9187 (TDD):edit:EJKolbe:1/27/99
RDI:FGriffith:BrCh:1/27/99.



October 12, 2001

Document Processing Desk (FPL)
Office of Pesticide Programs (H7504C)
U.S. Environmental Protection Agency
Ariel Rios Building
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Attn: Mr. Thomas Harris (IRB)

**SUBJECT: EMAMECTIN BENZOATE TECHNICAL
EPA REG. NO. 100-902
SUBMISSION OF FINAL PRINTED VERSION OF LABELING**

Syngenta Crop Protection is submitting 3 copies of the final printed version of labeling as requested in the EPA approval letter of September 13, 2001. The statement "See additional precautionary statements on label" has been added.

If you have any questions please contact me at (336) 632 7567.

Sincerely,

A handwritten signature in black ink, appearing to read "John L. Hott".

John L. Hott, Ph.D.
Regulatory Product Manager
Regulatory Affairs

Enclosures: 3 copies of final printed label

241

NOT REVIEWED
In Accordance with PR Notice 82-2
Based on Draft Labeling Dated

9/13/01

Emamectin Benzoate Technical

An Insecticide For Formulation Into End-Use Insecticide Products
Intended For Non-Domestic Food, Feed, and Outdoor Use – Head
and Stem Brassica Vegetables, Celery, and Head Lettuce

| | |
|--|--------|
| Active Ingredient: | |
| Emamectin Benzoate (CAS No. 155569-91-8) | 97.0% |
| Other Ingredients: | 3.0% |
| Total: | 100.0% |

Product of Switzerland

EPA Reg. No. 100-902

EPA Est. 41448-SW-1

Product ID. **28075**

KEEP OUT OF REACH OF CHILDREN.



**DANGER / PELIGRO
POISON**



Si usted no entiende la etiqueta, busque a alguien para que se la
explique a usted en detalle. (If you do not understand the label, find
someone to explain it to you in detail.)

See additional precautionary statements on label. *added*

Lot # _____
Net Weight: _____
Physical _____ kg
Assay _____ kg
Drum No. _____

SCP 902A-L1F 0901

syngenta



Emamectin Benzoate Technical

| FIRST AID | |
|---|--|
| If in eyes | <ul style="list-style-type: none"> • Hold eye open and rinse slowly and gently with water for 15-20 minutes. • Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. • Call a poison control center or doctor for treatment advice. |
| If on skin or clothing | <ul style="list-style-type: none"> • Take off contaminated clothing. • Rinse skin immediately with plenty of water for 15-20 minutes. • Call a poison control center or doctor for treatment advice. |
| If inhaled | <ul style="list-style-type: none"> • Move person to fresh air. • If person is not breathing, call 911 or an ambulance, and then give artificial respiration, preferably mouth-to-mouth, if possible. • Call a poison control center or doctor for treatment advice. |
| If swallowed | <ul style="list-style-type: none"> • Call a poison control center or doctor immediately for treatment advice. • Have person sip glass of water if able to swallow. • Do not induce vomiting unless told to do so by a poison control center or doctor. • Do not give anything by mouth to an unconscious person. |
| NOTE TO PHYSICIAN Recommendations for Medical Treatment for Emamectin Benzoate Acute Toxicity: Early signs of intoxication include mydriasis (dilated pupils), ataxia (unsteadiness), and muscle tremors. Toxicity following accidental ingestion of the concentrate can be minimized by inducing vomiting within 1/2 hour of exposure. If toxicity from exposure has progressed to cause severe vomiting, the extent of resultant fluid and electrolyte imbalance should be gauged. Appropriate supportive parenteral fluid replacement therapy should be given, along with other required supportive measures (such as maintenance of blood pressure levels) as indicated by clinical signs, symptoms, and measurements. In severe cases, observations should continue for at least several days until clinical condition is stable and normal. Since emamectin benzoate is believed to enhance GABA activity in animals, it is probably wise to avoid drugs that enhance GABA activity (barbiturates, benzodiazepines, valproic acid) in patients with potentially toxic emamectin benzoate exposure. | |
| Have the product container or label with you when calling a poison control center or doctor, or going for treatment. | |
| HOT LINE NUMBER For 24 Hour Medical Emergency Assistance (Human or Animal) or Chemical Emergency Assistance (Spill, Leak, Fire, or Accident), Call 1-800-888-8372 | |

PRECAUTIONARY STATEMENTS

Hazards to Humans and Domestic Animals

Corrosive. Causes irreversible eye damage. Do not get in eyes or on clothing. Wear protective eyewear (goggles, face shield, or safety glasses). May be fatal if swallowed. Wash thoroughly with soap and water after handling and before eating, drinking, or using tobacco. Remove and wash contaminated clothing before reuse.

Environmental Hazards

This pesticide is toxic to fish, birds, mammals, and aquatic invertebrates. Do not discharge effluent containing this active ingredient into lakes, streams, ponds, estuaries, oceans, or other public waters, unless in accordance with the requirements of a National Pollutant Discharge Elimination System (NPDES) permit, and the permitting authority has been notified in writing prior to discharge. Do not discharge effluent containing this product into sewer systems without previously notifying the local sewage treatment plant authority. For guidance, contact your State Water Board or Regional Office of the EPA.

CONDITIONS OF SALE AND LIMITATION OF WARRANTY AND LIABILITY

NOTICE: Read the entire Directions for Use and Conditions of Sale and Limitation of Warranty and Liability before buying or using this product. If the terms are not acceptable, return the product at once, unopened, and the purchase price will be refunded.

Emamectin Benzoate Technical

The Directions for Use of this product should be followed carefully. It is impossible to eliminate all risks inherently associated with the use of this product. Crop injury, ineffectiveness or other unintended consequences may result because of such factors as manner of use or application, weather or crop conditions, presence of other materials or other influencing factors in the use of the product, which are beyond the control of SYNGENTA CROP PROTECTION, Inc. or Seller. All such risks shall be assumed by Buyer and User, and Buyer and User agree to hold SYNGENTA and Seller harmless for any claims relating to such factors.

SYNGENTA warrants that this product conforms to the chemical description on the label and is reasonably fit for the purposes stated in the Directions for Use, subject to the inherent risks referred to above, when used in accordance with directions under normal use conditions. This warranty does not extend to the use of the product contrary to label instructions, or under abnormal conditions or under conditions not reasonably foreseeable to or beyond the control of Seller or SYNGENTA, and Buyer and User assume the risk of any such use. SYNGENTA MAKES NO WARRANTIES OF MERCHANTABILITY OR OF FITNESS FOR A PARTICULAR PURPOSE NOR ANY OTHER EXPRESS OR IMPLIED WARRANTY EXCEPT AS STATED ABOVE.

In no event shall SYNGENTA or Seller be liable for any incidental, consequential or special damages resulting from the use or handling of this product. **THE EXCLUSIVE REMEDY OF THE USER OR BUYER, AND THE EXCLUSIVE LIABILITY OF SYNGENTA AND SELLER FOR ANY AND ALL CLAIMS, LOSSES, INJURIES OR DAMAGES (INCLUDING CLAIMS BASED ON BREACH OF WARRANTY, CONTRACT, NEGLIGENCE, TORT, STRICT LIABILITY OR OTHERWISE) RESULTING FROM THE USE OR HANDLING OF THIS PRODUCT, SHALL BE THE RETURN OF THE PURCHASE PRICE OF THE PRODUCT OR, AT THE ELECTION OF SYNGENTA OR SELLER, THE REPLACEMENT OF THE PRODUCT.**

SYNGENTA and Seller offer this product, and Buyer and User accept it, subject to the foregoing Conditions of Sale and Limitations of Warranty and of Liability, which may not be modified except by written agreement signed by a duly authorized representative of SYNGENTA.

DIRECTIONS FOR USE

It is a violation of Federal law to use this product in a manner inconsistent with its labeling.

This product may be used only to manufacture/formulate other insecticide products registered and labeled for use on head and stem Brassica vegetables, celery, and head lettuce.

STORAGE AND DISPOSAL

Do not store near food or feed. Do not contaminate water, food, or feed by storage or disposal.

Store in a tightly closed original container in a cool, dry place.

Pesticide Disposal

Pesticide wastes are acutely hazardous. Improper disposal of excess pesticide, or rinsate is a violation of Federal law. If these wastes cannot be disposed of by use according to label instructions, contact your State Pesticide or Environmental Control Agency, or the Hazardous Waste representative at the nearest EPA Regional Office for guidance. Pesticide that cannot be used or chemically reprocessed must be disposed of according to federal, state, or local procedures under the Resource Conservation and Recovery Act.

Container Disposal

Triple rinse (or equivalent). Then offer for recycling or reconditioning, or puncture and dispose of in a sanitary landfill, or by other procedures approved by state and local authorities.

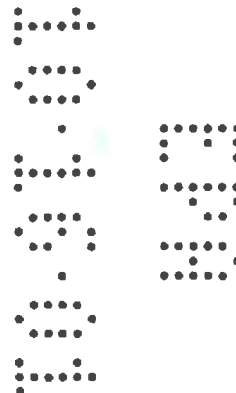
Note: For minor spills, leaks, etc. follow all precautions indicated on this label and clean up immediately. Take special care to avoid contamination of equipment and facilities during cleanup procedures and disposal of wastes.

©2001 Syngenta

For non-emergency (e.g., current product information),
call Syngenta Crop Protection, Inc. at 1-800-334-9481.

Syngenta Crop Protection, Inc.
Greensboro, North Carolina 27409
www.syngenta-us.com

SCP 902A-L1F 0901





UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

SEP 13 2001

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Carolyn Brinkley
Syngenta Crop Protection, Inc.
PO Box 18300
Greensboro, NC 27419

*old 3/12/86 memo² "Hatched"
concerned
avermectin but 7 extended
concept to emamectin
- T. H. Lamb*

re: Enamectin Benzoate Technical, EPA Reg. # 100-902
revised basic and alternate CSF dated 8/27/01
amended label submitted 8/29/01 and revised 9/12/01
accepted

Dear Ms. Brinkley:

The Agency has reviewed your submission for revised Confidential Statements of Formula (CSF) along with new product chemistry data (MRID 454208-01). A initial review of these data noting several deficiencies was previously sent with EPA's letter from me dated 8/21/01. Enclosed please find a copy of the review by Linda Kutney dated 9/11/01 of your 8/29/01 revised submission.

The Confidential Statements of Formula dated 8/27/01 for the basic and alternate formulations are **ACCEPTED**. Revised ingredients were found to be similar to previous ingredients. The ingredient percentages and limits comply with PR Notice 91-2. The basic and alternate Confidential Statements of Formula have been added to your file as part of the record. These replace all previous versions.

The Agency has also reviewed the label amendment associated with these new CSFs. Among other items, the label changes the percentage of active ingredient of the product and moves the impurities previously listed as related compounds under the "active ingredient" header to the "other ingredients" header. Since EPA is not concerned with the toxicology of the related impurities (memorandum by W. Dykstra 3/12/86 PP#5G3287/5H5474) and Syngenta is not claiming efficacy related to these compounds then EPA policy states that these impurities should be listed as "other" rather than "active".

The label submitted 8/29/01 and revised 9/12/01, submitted in connection with

Page 1 of 2

registration under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended, is **ACCEPTED** provided that you do the following:

- 1) Submit three (3) copies of your final printed labeling prior to releasing your product for shipment.
- 2) Submit a 5 gram sample of the new technical grade active ingredient as per Guideline 830.1900. This sample is required since the percentage active ingredient has changed since the initial registration. This sample must be submitted prior to releasing your product for shipment. The sample should be sent to:

Mr. Francis Griffith
EPA/OPP
Analytical Chemistry Laboratory
701 Mapes Road
Fort Mead, Maryland 20755-5350

If these provisions are not complied with the registration will be subject to cancellation in accordance with FIFRA Section 6(e). Your release for shipment of the product bearing the amended labeling constitutes acceptance of these conditions.

A copy of your label stamped "accepted" is enclosed for your records.

If you have any questions please contact me at (703) 308-9423 or harris.thomas@epa.gov.

Yours truly,



Thomas C. Harris, Biologist
Insecticide-Rodenticide Branch
Registration Division (7505C)

enclosure

cc: Francis Griffith



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MAR 12 1986

CONFIDENTIAL

MEMORANDUM:

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: PP# 5G3287/5H5474; Avermectin (Abamectin)
in/on citrus; Deferral from RCB; "Confidential"
Record No. 164515/164516
Caswell No. 63AB
Project No. 1071/1072

TO: George LaRocca
Product Manager (15)
Registration Division (TS-767)
and
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

THRU: Edwin Budd, Section Head
Review Section II
Toxicology Branch
Hazard Evaluation Division (TS-769)

FROM: William Dykstra
Toxicology Branch
Hazard Evaluation Division (TS-769)

William Dykstra

*Budd
2/27/86*

*def WBS
3/11/86*

2/27/86

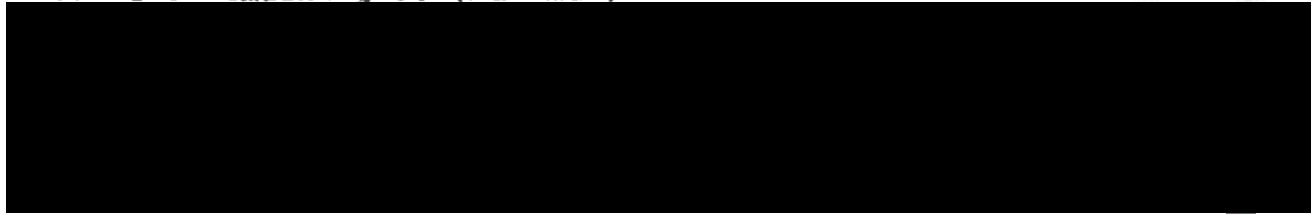
*Copy -
not included w/
9/13/01 letter since
not returned yet
from FRC*

Requested Action:

In the RCB review of the temporary tolerances for Abamectin in citrus (12/19/85 from L. Cheng to G. LaRocca), RCB defers to Toxicology Branch "as to the toxicological significance of the identified and unidentified impurities in the technical material." This memo addresses the RCB deferral.

Background: "Confidential"

As stated in the confidential appendix of the RCB review (above). "The technical material is 95% pure AVM-B1 (minimum). It is mixture of >80% avermectin B 1a plus >20% avermectin B 1b. The remaining 5% (maximum) is a mixture of other avermectins:



CONFIDENTIAL

On an acute oral LD₅₀ basis, infant rats of both sexes are the most sensitive animals. The oral LD₅₀ is 1.52 mg/kg with 95% confidence levels between 1.05 and 2.19 mg/kg. Abamectin is teratogenic in mice (cleft palate and anophthalmia) at 0.8 mg/kg/day. The NOEL for these effects is 0.2 mg/kg/day.

Abamectin was not teratogenic in rats up to 1.6 mg/kg/day and rabbits up to 2.0 mg/kg.

In a ten day oral gavage study with pregnant mice, one mouse died at 0.075 mg/kg/day after four doses. The NOEL for lethality is 0.05 mg/kg/day in pregnant mice in this 10 day study.

Additionally, the NOEL for a 21 dermal toxicity study in rabbits is 125 mg/kg/day.

Abamectin was not mutagenic in the Ames assay and in vivo bone marrow cytogenetics. In rat hepatocytes, Abamectin caused an induction of single strand DNA breaks in vitro. No effect was observed when this same assay was carried out in hepatocytes from rats dosed in vivo at the LD₅₀ (10.6 mg/kg).

In the mammalian cell mutagenic assay, Abamectin was not mutagenic for V-79 cells. The compound does not sensitize skin. The metabolic T 1/2 is 1.2 days. Two metabolites of Abamectin have an oral LD₅₀ in mice of 48 and 5000 mg/kg.

No antidote for Abamectin is available. Precautionary labelling recommends induction of vomiting as a method of practical treatment.

Conclusion:

Since the 5% of identified impurities (mixture of other avermectins) and 1% of unidentified impurities of Abamectin are found in the technical material, these impurities (together with the technical) would have been toxicologically characterized in the studies performed using Abamectin. Toxicology Branch concludes that the impurities in Abamectin are not of toxicological concern at this time.

Review:

1. No new toxicity data were submitted.

Enamectin Benzoate Technical

An insecticide for formulation into end-use insecticide products intended for non-domestic food, feed, & outdoor use – head & stem Brassica vegetables, celery & head lettuce

Active Ingredient:

Enamectin Benzoate (CAS No. 155569-91-8) _____ 97.0%

Other Ingredients: _____ 3.0%

Total: _____ 100.0%

Product of Switzerland

EPA Reg. No. 100-902

EPA Est.

Lot# _____

Net Weight: _____

Physical _____ kg

Assay _____ kg

Drum No. _____

KEEP OUT OF REACH OF CHILDREN

SKULL & CROSSBONES]

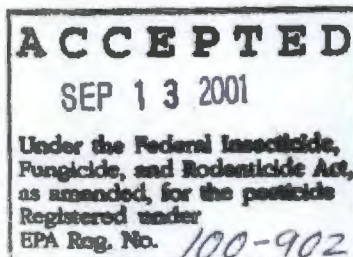
DANGER/PELIGRO

[SKULL & CROSSBONES]

POISON

[red type]

Si usted no entiende la etiqueta, busque a alguien para que se la explique a usted en detalle. (If you do not understand the label find someone to explain it to you in detail.)



PRECAUTIONARY STATEMENTS

Hazards to Humans and Domestic Animals

Corrosive. Causes irreversible eye damage. Do not in eyes or on clothing. Wear protective eyewear (goggles, face shield, or safety glasses) May be fatal if swallowed. Wash thoroughly with soap and water after handling and before eating, drinking, or using tobacco. Remove and wash contaminated clothing before reuse.

Have the product container or label with you when calling a poison control center or doctor or going for treatment.

| FIRST AID | |
|---|---|
| If in eyes | <ul style="list-style-type: none">• Hold eye open and rinse slowly and gently with water for 15-20 minutes.• Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye.• Call a poison control center or doctor for treatment advice |
| If on skin or clothing | <ul style="list-style-type: none">• Take off contaminated clothing.• Rinse skin immediately with plenty of water for 15-20 minutes• Call a poison control center or doctor for treatment advice. |
| If inhaled | <ul style="list-style-type: none">• Move person to fresh air• If person is not breathing, call 911 or an ambulance, and then give artificial respiration, preferably mouth-to-mouth, if possible.• Call a poison control center or doctor for treatment advice |
| If swallowed | <ul style="list-style-type: none">• Call a poison control center or doctor immediately for treatment advice• Have a person sip a glass of water if able to swallow• Do not induce vomiting unless told to do so by a poison control center or doctor.• Do not give anything by mouth to an unconscious person. |
| HOT LINE NUMBER | |
| In the event of a major fire, spill, or other emergency call 1-800-888-8372 day or night. | |

NOTE TO PHYSICIAN

Recommendations for Medical Treatment for Emamectin Benzoate Acute Toxicity:

Early signs of intoxication include mydriasis (dilated pupils), ataxia (unsteadiness), and muscle tremors. Toxicity following accidental ingestion of the concentrate can be minimized by inducing vomiting within ½ hour of exposure. If toxicity from exposure has progressed to cause severe vomiting, the extent of resultant fluid and electrolyte imbalance should be gauged. Appropriate supportive parenteral fluid replacement therapy should be given, along with other required supportive measures (such as maintenance of blood pressure levels) as indicated by clinical signs, symptoms, and measurements. In severe cases, observations should continue for at least several days until clinical condition is stable and normal. Since emamectin benzoate is believed to enhance GABA activity in animals, it is probably wise to avoid drugs that enhance GABA activity (barbiturates, benzodiazepines, valproic acid) in patients with potentially toxic emamectin benzoate exposure. For 24 emergency medical information, call Syngenta Crop Protection, Inc. at 1-800-888-8372.

Environmental Hazards

This pesticide is toxic to fish, birds, mammals, and aquatic invertebrates. Do not discharge effluent containing this active ingredient into lakes, streams, ponds, estuaries, oceans, or other public waters, unless in accordance with the requirements of a National Pollutant Discharge Elimination System (NPDES) permit, and the permitting authority has been notified in writing prior to discharge. Do not discharge effluent containing this product into sewer systems without previously notifying the local sewage treatment plant authority. For guidance, contact your State Water Board or Regional Office of the EPA.

CONDITIONS OF SALE AND LIMITATION OF WARRANTY AND LIABILITY

NOTICE: Read the entire Directions for Use and Conditions of Sale and Limitation of Warranty and Liability before buying or using this product. If the terms are not acceptable, return the product at once, unopened, and the purchase price will be refunded.

The Directions for Use of this product should be followed carefully. It is impossible to eliminate all risks inherently associated with the use of this product. Crop injury, ineffectiveness or other unintended consequences may result because of such factors as manner of use or application, weather or crop conditions, presence of other materials or other influencing factors in the use of the product, which are beyond the control of SYNGENTA CROP PROTECTION, Inc. or Seller. All such risks shall be assumed by Buyer and User, and Buyer and User agree to hold SYNGENTA and Seller harmless for any claims relating to such factors.

SYNGENTA warrants that this product conforms to the chemical description on the label and is reasonably fit for the purposes stated in the Directions for Use, subject to the inherent risks referred to above, when used in accordance with directions under normal use conditions. This warranty does not extend to the use of the product contrary to label instructions, or under abnormal conditions or under conditions not reasonably foreseeable to or beyond the control of Seller or SYNGENTA, and Buyer and User assume the risk of any such use. SYNGENTA MAKES NO WARRANTIES OF MERCHANTABILITY OR OF FITNESS FOR A PARTICULAR PURPOSE NOR ANY OTHER EXPRESS OR IMPLIED WARRANTY EXCEPT AS STATED ABOVE.

In no event shall SYNGENTA or Seller be liable for any incidental, consequential or special damages resulting from the use or handling of this product. **THE EXCLUSIVE REMEDY OF THE USER OR BUYER, AND THE EXCLUSIVE LIABILITY OF SYNGENTA AND SELLER FOR ANY AND ALL CLAIMS, LOSSES, INJURIES OR DAMAGES (INCLUDING CLAIMS BASED ON BREACH OF WARRANTY, CONTRACT, NEGLIGENCE, TORT, STRICT LIABILITY OR OTHERWISE) RESULTING FROM THE USE OR HANDLING OF THIS PRODUCT, SHALL BE THE RETURN OF THE PURCHASE PRICE OF THE PRODUCT OR, AT THE ELECTION OF SYNGENTA OR SELLER, THE REPLACEMENT OF THE PRODUCT.**

SYNGENTA and Seller offer this product, and Buyer and User accept it, subject to the foregoing conditions of sale and limitations of warranty and of liability, which may not be modified except by written agreement signed by a duly authorized representative of SYNGENTA.

DIRECTIONS FOR USE

It is a violation of Federal law to use this product in a manner inconsistent with its labeling.

This product may be used only to manufacture/formulate other insecticide products registered and labeled for use on head and stem Brassica vegetables, celery, and head lettuce.

STORAGE AND DISPOSAL

Do not store near food or feed. Do not contaminate water, food, or feed by storage or disposal.

Store in a tightly closed original container in a cool, dry place.

Pesticide Disposal

Pesticide wastes are acutely hazardous. Improper disposal of excess pesticide, or rinsate is a violation of Federal law. If these wastes cannot be disposed of by use according to label instructions, contact your State Pesticide or Environmental Control Agency, or the Hazardous Waste representative at the nearest EPA Regional Office for guidance. Pesticide that cannot be used or chemically reprocessed must be disposed of according to federal, state, or local procedures under the Resource Conservation and Recovery Act.

Container Disposal**Bulk**

Thoroughly clean container before reuse. Consult federal, state, or local disposal authorities for approved alternative procedures.

250 Gal Mini Bulk

This is a refillable container that must be returned to an authorized Syngenta refilling facility for refilling or disposal.

Other Containers

Triple rinse (or equivalent). Then offer for recycling or reconditioning, or puncture and dispose of in a sanitary landfill, or by other procedures approved by state and local authorities.

Note: For minor spills, leaks, etc. follow all precautions indicated on this label and clean up immediately. Take special care to avoid contamination of equipment and facilities during cleanup procedures and disposal of wastes. **In the event of a major spill, fire, or other emergency, call 1-800-888-8372, day or night.**

| |
|---|
| For non-emergency (e.g. current product information) call Syngenta Crop Protection, Inc. at 1-800-334-9481 |
|---|

©2001 Syngenta

Syngenta Crop Protection, Inc.
Greensboro, North Carolina 27409

SCP

August 30, 2001 –draft
revised label to EPA,
revised first aid statements
according to PR Notice
2000-3, revised ingredient
statement according to new
CSF and prod. chem,
revised and added storage
and disposal statements,
specified on front panel end-
use product uses supported
for this active ingredient.
Corrected label by adding
Spanish signal word and
warning statement, deleted
chemical name of active –
common name and CAS no.
are sufficient, changed all
references to Novartis to
Syngenta and replaced
Warranty statement with
new Syngenta Warranty
Statement, changed country
of origin to Switzerland,
revised ingredient statement
per PR Notices 97-5 & 97-6

LG- 9/12/01



lorraine.gold@syngen
ta.com

09/12/2001 03:10
PM

To: Thomas Harris/DC/USEPA/US@EPA
cc: john.hott@syngenta.com
Subject: corrections to label for 100-902

Mr. Harris, As per your request find attachments, in WORD and Pdf format of the corrected label for Emamectin Benzoate Technical, Reg. No. 100-902. If I can be of any more help please contact me.

Rainy Gold
Label Specialist
Regulatory Affairs Department
Syngenta Crop Protection, Inc.
336-632-2852

-----Original Message-----

From: Harris.Thomas@epamail.epa.gov
[mailto:Harris.Thomas@epamail.epa.gov]
Sent: Wednesday, September 12, 2001 12:12 PM
To: Hott John USGR
Cc: Brinkley Carolyn USGR
Subject: ASAP: need fixes to 100-902 label

John,

Linda has reviewed your revised CSF for 100-902 (and did an incredible job completing it yesterday despite events). It will be approved BUT I have a couple of important changes that need to be made to the label submitted 8/29/01 before I can formally accept the CSF and label. I can wrap this up as soon as you can get me a corrected label. If you want, you can email me the revised label (either in WordPerfect or PDF format) along with a cover note in the text field of the email (just replying with history to this email would be good). I will print the email and file as a revision to the currently open paper submission.

Changes required:

- 1) Front panel, ingredients statement: Change CAS number from 137512-74-4 to 155569-91-8. You have the correct number on the CSF. 155... is a newer CAS number that replaces the older 137... number.
- 2) Storage and Disposal, Pesticide Disposal: Remove the blanks indicated by underlines. Your intention was to indicate that you have removed some words from the previous label. That's fine for the marked-up version of the label but the blanks should not appear on the clean copy of the proposed label that I'll stamp since it makes it look like there is information that needs to be added to these areas.

I'm scheduled to be out Thursday afternoon and Friday but if you can get me this change first thing on Thursday (9/13) morning I'll get it out before I leave (otherwise first thing on Monday).

Tom Harris
EPA/OPPTS/OPP/RD/IRB
(703) 308-9423
harris.thomas@epa.gov



emamectin.pdf



EmamectinDraftRev9.12.01.doc



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

OPPTS/OPP/RD/TRB/PRODUCT CHEMISTRY TEAM

WASHINGTON, D.C. 20460

DATE: 11/SEP/2001

SUBJECT: PRODUCT CHEMISTRY REVIEW OF MP ☐ EP ☐ TECHNICAL ☒

DP BARCODE No.: D277757

REG./File Symbol: 100-902

PRODUCT NAME: Emamectin Benzoate Technical (MK-244)

COMPANY: Syngenta Crop Protection, Inc.

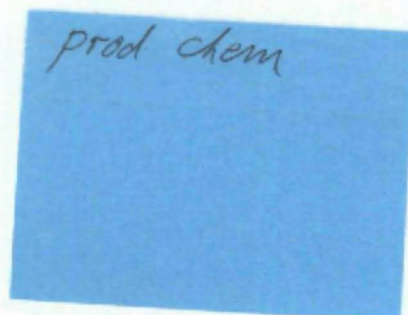
FROM: Linda L. Kutney, Chemist
Product Chemistry Team
Technical Review Branch/RD (7505C)

Linda L. Kutney
9/11/01

TO: Deborah McCall, Thomas Harris PM 4
Insecticide Rodenticide Branch/RD(7505C)

Syngenta Crop Protection, Inc., in a letter dated 5/18/01, submitted data intended to support registration of their product "Technical Emamectin Benzoate," also referred to as MK-244 of Avermectin. Reg. No. 100-902, containing a nominal concentration of 97.0% Emamectin Benzoate. The product was previously registered by Merck and has been transferred to Syngenta, who will be producing it in the future. New product chemistry data, new analytical methods and a new CSF was submitted, with MRID Nos. 454208-01. A basic proposed CSF, dated 5/1/01 was also submitted. These data were reviewed by TRB under D276416, on 8/17/01 and deficiencies were noted.

Syngenta has now responded to deficiencies listed in TRB's 8/17/01 review, subsequent to several conversations with the Agency and a conference call on 8/23/01 between the reviewer and Mr. Tom Harris of RD, and Syngenta's Ms. Carolyn Brinkley (336-632-2838). Dr. Johnny Reynolds, and Mr. John Hobb. This submission, sent with a letter dated 8/29/01, included an updated label pinpunched 8/30/01, and updated basic and alternate CSI's, both dated 8/27/01.



Previous deficiencies are listed separately by number below, along with Syngenta's Response and the Current Agency Conclusion.

1. *The nominal concentration of the Emamectin Benzoate a.i. on the proposed 5/1/01 CSF does not agree with the label concentration, in accordance with the requirements of PR 91-2.*

Syngenta's Response

The nominal concentration of the Emamectin Benzoate a.i. on the proposed 8/27/01 basic and alternate CSFs now agrees with the concentration on the updated label, pinpunched 8/30/01.

Agency Conclusion

This deficiency is resolved.

2. *The label statement concerning process related impurities and inert ingredients is not consistent with the CSF. The label must be revised.*

Syngenta's Response

Syngenta has proposed revised 8/27/01 basic and alternate CSFs and a revised label.

Agency Conclusion

The revised label now states that Emamectin Benzoate technical contains 97.0% Emamectin Benzoate ai and 3.0 % other ingredients. This is agreement with the % ai and "other ingredients" listed on the revised CSF. This deficiency is resolved.

3. *All impurities present at levels of 0.1% or greater must be identified on the CSF.*

Syngenta's Response

Syngenta has quantified all of the process related impurities possible.

Agency Conclusion

The impurities are sufficiently identified, and the total % by wt is now 100%. This deficiency is resolved.

4. *Syngenta must update their label to reflect the fact that they are replacing Merck as the Registrant.*

Syngenta's Response

Syngenta's name is on the current label.

Agency Conclusion

This deficiency is resolved.

5. *Syngenta must ensure that the sum of all of the components in the CSF, % by weight, in column 13b, total 100.0%.*

Syngenta's Response

Syngenta revised the % process related impurities slightly, by 0.1%, and the %'s by weight in column 13b are now 100.0%.

Agency Conclusion

This deficiency is resolved.

6. *Column 11 of the proposed 5/1/01 CSF should give the full supplier name and street address for all components in the label, except for the impurities* [REDACTED]

Syngenta's Response

The supplier name and street address for the ai is given on the top of the CSF.

Agency Conclusion

This deficiency is resolved.

7. *Guideline 830.1550, product identity and composition requirements are not acceptable, but may be satisfied by addressing the deficiencies concerning the CSF and label.*

Agency Conclusion

The revised CSF and label are in agreement and are acceptable. This deficiency is resolved.

8. *Guideline 830.1750, certified limits, is not satisfied because impurities present over 0.1% must all be listed on the CSF. The total of all values for %-by-weight in column 13b must be 100.0%. The certified limits for Emamectin Benzoate ai are slightly wider than the standard limits specified in, but are acceptable.*

Agency Conclusion

Syngenta revised the %process related impurities slightly, by 0.1%, and the %'s by weight in column 13b are now 100.0%. Guideline 830.1750 is satisfied.

9. *Guideline 830.1900, Submittal of Samples, is required for integrated products and for those of toxicological concern, as well as for nonintegrated products with interference or method problems, etc. A sample of the tga1 will be required prior to its registration.*

Syngenta's Response

Syngenta has acknowledged this requirement in the telephone conference.

Agency Conclusion

This deficiency is resolved. The samples must be sent to Mr Richard Griffith at the EPA Laboratory in Fort Mead, Maryland, at the following address:

Mr Richard Griffith
EPA
Analytical Chemistry Laboratory
701 Mapes Road
Fort Mead, Maryland 20755-5350

Mr. Griffith may be contacted at 1-410-305-2905, for more specific instructions.

OVERALL CONCLUSION:

TRB accepts the proposed basic and alternate CSFs, dated 8/27/01. In addition, the label concentration for Emamectin Benzoate ai is now 97.0%, and the "other ingredients are now labeled 3.0%," in accordance with current Agency policies. The proposed basic and alternate CSFs, dated 8/27/01, are acceptable from a TRB, product chemistry standpoint.

The proposed label, however, cannot be considered acceptable until Syngenta adequately completes the storage and disposal section (at a minimum, they must fill in the blanks). The Agency must recheck the label prior to its acceptance.

DP BARCODE: D277757

CASE: 046738
SUBMISSION: S603095

DATA PACKAGE RECORD
BEAN SHEET

DATE: 09/10/01
Page 1 of 1

* * * CASE/SUBMISSION INFORMATION * * *

CASE TYPE: REGISTRATION ACTION: 346 RESUBMISSION
RANKING : 5 POINTS ()
CHEMICALS: 122806 4''-Epimethylamino-4''-deoxyavermectin B1a and B1b 95.0000%

ID#: 000100-00902 EMAMECTIN BENZOATE TECHNICAL
COMPANY: 000100 SYNGENTA CROP PROTECTION, INC.
PRODUCT MANAGER: 04 TINA LEVINE 703-308-7055 ROOM: CM2 219
PM TEAM REVIEWER: THOMAS HARRIS 703-308-9423 ROOM: CM2 211
RECEIVED DATE: 08/30/01 DUE OUT DATE: 11/28/01

* * * DATA PACKAGE INFORMATION * * *

DP BARCODE: 277757 EXPEDITE: Y DATE SENT: 09/10/01 DATE RET.: / /
CHEMICAL: 122806 4''-Epimethylamino-4''-deoxyavermectin B1a and B1b benzoate
TYPE: 001

| ASSIGNED TO | DATE | IN | DATE | OUT | ADMIN DUE DATE: 10/25/01 |
|-------------|------|----|------|-----|--------------------------|
| DIV : RD | / | / | / | / | NEGOT DATE: / / |
| BRAN: TRB | / | / | / | / | PROJ DATE: / / |
| SECT: CHEM | / | / | / | / | |
| REVR : | / | / | / | / | |
| CONTR: | / | / | / | / | |

* * * DATA REVIEW INSTRUCTIONS * * *

EMAMECTIN

revised CSF per EPA comments in LKutney 8/17/01 review and subsequent meetings.

Please review to see if changes made as agreed upon. If ok, write acceptance review. Thanks

-Tom Harris
RD/IRB
308-9423
213 CM2

* * * DATA PACKAGE EVALUATION * * *

No evaluation is written for this data package

* * * ADDITIONAL DATA PACKAGES FOR THIS SUBMISSION * * *

| DP BC | BRANCH/SECTION | DATE OUT | DUE BACK | INS | CSF | LABEL |
|-------|----------------|----------|----------|-----|-----|-------|
|-------|----------------|----------|----------|-----|-----|-------|



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

08/30/2001

CAROLYN F. BRINKLEY
SYNGENTA CROP PROTECTION, INC.
P.O. BOX 18300
GREENSBORO NC 274198300

OFFICE OF
RESEARCH AND DEVELOPMENT

PRODUCT NAME: EMAMECTIN BENZOATE TECHNICAL
COMPANY NAME: SYNGENTA CROP PROTECTION, INC.
OPP IDENTIFICATION NUMBER: 286563
EPA REGISTRATION NUMBER: 100-902
EPA RECEIPT DATE: 08/30/2001

SUBJECT: RECEIPT OF AMENDMENT

DEAR REGISTRANT:

The Office of Pesticide Programs has received your application for an amendment and it has passed an administrative screen for completeness.

During the initial screen we determined that the application qualifies for fast track review. The package will now be forwarded to the Product Manager for review to determine its acceptability.

If you have any questions, please contact Insecticide Branch, Product Manager 03, at (703) 305-6891.

Sincerely,

A handwritten signature in cursive script, appearing to read "J. White".

Front End Processing Staff
Information Services Branch
Program Management and Support Division



Syngenta Crop Protection, Inc Tel 336 632 6000
P.O. Box 18300
Greensboro, NC 27419-8300

Carolyn F. Brinkley
Sr. Regulatory Product Manager
Syngenta Crop Protection, Inc
Phone (336) 632-2838
Fax (336) 292-6374
E-mail: carolyn.brinkley@syngenta.com

Via hand delivery

August 29, 2001

Mr. Thomas Harris
U.S. Environmental Protection Agency
Office of Pesticide Programs
Arlington, VA

**SUBJECT: EMAMECTIN BENZOATE TECHNICAL
EPA REG. NO. 100-902
PENDING FORMULATION CHANGE**

**(1) REVISED CSF BASED ON COMMENTS FROM EPA CHEMISTRY
REVIEWER
(2) REVISED LABEL**

Dear Mr. Harris:

Based on the EPA's recent review of the revised confidential statement of formula and the supporting product chemistry data for Emamectin Benzoate Technical, we made additional changes to the CSF and a copy is enclosed with this letter. In addition, because the percentage of the active ingredient has changed, we revised the **label ingredient statement**. In addition to that revision, we also included these changes to the label:

1. Changed all references to Novartis to Syngenta and replaced the Warranty Statement with the new **Syngenta Warranty Statement**.
2. Revised the ingredient statement as follows.
 - a. Omitted the chemical name and changed **Inert Ingredients** to **Other Ingredients** as permitted by EPA PR Notices 97-5 and 97-6
 - b. Changed the ingredient statement as follows:
 1. changed the **percent active ingredient** from 96% to 97%
 2. omitted "**Related Compounds**" and added their percentage into "Other Ingredients" which has been changed to 3.0%

Justification for this change:

Although there are other avermectins in this product, Syngenta does not have any data that would indicate they have any pesticidal activity. Thus we have deleted "**Related Compounds**" from the ingredient statement. Here is the justification for this change: The EPA's Label Review Manual Chapter 6, Page 5 states: "If one or more related compounds is pesticidal to the target pest, it

must be included under the **Active Ingredient** heading. Related compounds with no determined active/inert status must be included under the total percentage of the Inert [Other] Ingredient heading without designation as related compounds or by name. (PR-81-4)

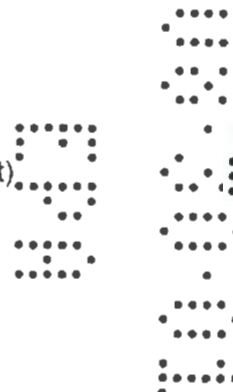
- c. Revised the **first aid statements** per PR Notice 2000-3.
- d. Corrected the Danger **signal word** to include "Peligro" and the Spanish warning statement. Note that the signal word will be in Red on the label.
- e. Revised the **storage statements** to include EPA-required language.
- f. Added additional disposal statements to cover several types of containers. In addition we deleted reference to "spray mixture" in the **Pesticide Disposal** section because this is a technical product and it is not sprayed.
- g. Specified on the **front panel** of the label that this product can be used for formulation into end-use insecticide products intended for non-domestic food, feed, and outdoor use – head and stem Brassica vegetables, celery, and head lettuce.
- h. Changed the **country of origin** from the US to Switzerland as required by US Customs.
- i. Put the "Recommendations for Medical Treatment....." into a box **labeled "NOTE TO PHYSICIAN"** as required for Category I products.
- j. Added "For non-emergency (e.g. current product information), call Syngenta Crop Protection, Inc at 1-800-334-9481.
- k. Changed the **copyright date**
- l. Listed a summary of the changes on the last page of the label for reference.

Thank you and Linda Kutney for reviewing our initial submission so promptly. We appreciate your willingness to review the revised CSF and label quickly as well. If you have any questions or comments, please contact me. I can be reached at (336) 632-2838.

Sincerely,


Carolyn F. Brinkley
Sr. Regulatory Product Manager
Regulatory Affairs

Enclosures: Revised CSF
Revised label (5 copies)
Revised label with revisions marked
Copy of current label
EPA Application for Pesticide Registration (Amendment)





United States
Environmental Protection Agency
Washington, DC 20460

| | |
|-------------------------------------|--------------|
| <input type="checkbox"/> | Registration |
| <input type="checkbox"/> | Amendment |
| <input checked="" type="checkbox"/> | Other |

OPP Identifier Number
~~269586~~
286563

Application for Pesticide - Section I

| | | |
|---|--|--|
| 1. Company/Product Number 100-902 | 2. EPA Product Manager Mr. Tom Harris 03 | 3. Proposed Classification <input checked="" type="checkbox"/> None <input type="checkbox"/> Restricted |
| 4. Company/Product (Name) | PM# Insecticide-Rodenticide Branch | |
| 5. Name and Address of Applicant (Include ZIP Code) Syngenta Crop Protection, Inc. P. O. Box 18300 Greensboro, NC 27419 <input type="checkbox"/> Check if this is a new address | 6. Expedited Review. In accordance with FIFRA Section 3(c)(3) (b)(I), my product is similar or identical in composition and labeling to: EPA Reg. No. _____ Product Name _____ | |

Section - II

| | |
|---|--|
| <input type="checkbox"/> Amendment - Explain below. | <input type="checkbox"/> Final printed labels in response to Agency letter dated _____ |
| <input checked="" type="checkbox"/> Resubmission in response to Agency review, verbal communication in Aug 2001 | <input type="checkbox"/> "Me Too" Application. |
| <input type="checkbox"/> Notification - Explain below. | <input type="checkbox"/> Other - Explain below. |

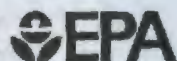
Explanation: Use additional page(s) if necessary. (For Section I and Section II.).
In May 2001 Syngenta submitted a revised CSF and supporting product chemistry data for Enamectin Benzoate Technical. In August, the reviewer and Tom Harris, Registration Division informed Syngenta that the CSF needed further revision. In addition, Syngenta was asked to submit a revised label for this product. The revised CSF is attached. The revised label is also attached and has a number of revisions : ingredient statement, addition of Spanish signal word and warning statement, revised storage and disposal statements, updated first aid statements per PR Notice 2000-3, all references to Novartis changed to Syngenta, new Syngenta warranty statement, and other minor editorial changes marked on one of the enclosed copies of the label.

Section - III

| | | | |
|--|---|---|--|
| 1. Material This Product Will Be Packaged in: | | | 2. Type of Container |
| Child-Resistant Packaging <input type="checkbox"/> Yes* <input type="checkbox"/> No | Unit Packaging <input type="checkbox"/> Yes <input type="checkbox"/> No | Water Soluble Packaging <input type="checkbox"/> Yes <input type="checkbox"/> No | <input type="checkbox"/> Metal <input type="checkbox"/> Plastic <input type="checkbox"/> Glass <input type="checkbox"/> Paper <input type="checkbox"/> Other (Specify) _____ |
| Certification must be submitted If "Yes" Unit Packaging wgt. No. per Container | | | If "Yes" Unit Packaging wgt. No. per container |
| 3. Location of Net Contents Information <input type="checkbox"/> Label <input type="checkbox"/> Container | 4. Size(s) Retail Container | 5. Location of Label Directions <input type="checkbox"/> On Label <input type="checkbox"/> On Labeling accompanying product | |
| 6. Manner in Which Label is Affixed to Product <input type="checkbox"/> Lithograph <input type="checkbox"/> Other _____ <input type="checkbox"/> Paper glued <input type="checkbox"/> Stenciled | | | |

Section - IV

| | | |
|---|---|--|
| 1. Contact Point (Complete items directly below for identification of individual to be contacted, if necessary, to process this application.) | | |
| Name Carolyn F. Brinkley for this action John Hott (for this action and future actions on this ai) | Title Sr. Regulatory Product Manager Regulatory Product Manager | Telephone No. (Include Area Code) 336-632-2838 336-682-7096 |
| 2. Signature <i>Carolyn F. Brinkley</i> | | 6. Date Application Received (Stamped) |
| 3. Title Sr. Regulatory Product Manager | | |
| 4. Typed Name Carolyn F. Brinkley | | |
| 5. Date August 29, 2001 | | |



United States
Environmental Protection Agency
Washington, DC 20460

☐ Registration
☐ Amendment
☐ Other

OPP Identifier Number

286563

Application for Pesticide - Section I

| | | |
|--|--|---|
| 1. Company/Product Number | 2. EPA Product Manager | 3. Proposed Classification <input type="checkbox"/> None <input type="checkbox"/> Restricted |
| 4. Company/Product (Name) | PM# | |
| 5. Name and Address of Applicant (Include ZIP Code) <input type="checkbox"/> Check if this is a new address | 6. Expedited Review. In accordance with FIFRA Section 3(c)(3) (b)(i), my product is similar or identical in composition and labeling to: EPA Reg. No. _____ Product Name _____ | |

Section - II

| | |
|--|--|
| <input type="checkbox"/> Amendment - Explain below. | <input type="checkbox"/> Final printed labels in response to Agency letter dated _____ |
| <input type="checkbox"/> Resubmission in response to Agency letter dated _____ | <input type="checkbox"/> "Me Too" Application. |
| <input type="checkbox"/> Notification - Explain below. | <input type="checkbox"/> Other - Explain below. |

Explanation: Use additional page(s) if necessary. (For section I and Section II.)

Section - III

| | | | | | |
|---|---|--|--|---|--|
| 1. Material This Product Will Be Packaged In: | | | | 2. Type of Container | |
| Child-Resistant Packaging <input type="checkbox"/> Yes* <input type="checkbox"/> No | Unit Packaging <input type="checkbox"/> Yes <input type="checkbox"/> No | Water Soluble Packaging <input type="checkbox"/> Yes <input type="checkbox"/> No | | <input type="checkbox"/> Metal | |
| | | | | <input type="checkbox"/> Plastic | |
| | | | | <input type="checkbox"/> Glass | |
| | | | | <input type="checkbox"/> Paper | |
| | | | | <input type="checkbox"/> Other (Specify) _____ | |
| 3. Location of Net Contents Information <input type="checkbox"/> Label <input type="checkbox"/> Container | | 4. Size(s) Retail Container | | 5. Location of Label Directions <input type="checkbox"/> On Label <input type="checkbox"/> On Labeling accompanying product | |
| 6. Manner in Which Label is Affixed to Product <input type="checkbox"/> Lithograph <input type="checkbox"/> Paper glued <input type="checkbox"/> Stenciled | | <input type="checkbox"/> Other _____ | | | |

Section - IV

| | | |
|---|----------|---|
| 1. Contact Point (Complete items directly below for identification of individual to be contacted, if necessary, to process this application.) | | |
| Name | Title | Telephone No. (Include Area Code) |
| Certification I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law. | | 6. Date Application Received (Stamped) |
| 2. Signature | 3. Title | |
| 4. Typed Name | 5. Date | |

PAPERWORK REDUCTION ACT NOTICE and INSTRUCTIONS

PAPERWORK REDUCTION ACT NOTICE: Public reporting burden for this collection of information is estimated to average 0.85 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding the burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Chief, Information Policy Branch, (2135), U.S. Environmental Protection Agency, 401 M Street, SW, Washington, DC 20460.

INSTRUCTIONS: This form is to be used for all applications for new registration, and use reregistration, amendment, resubmission, to applications for notifications, final printed labeling, reregistration, etc. In order to process an application for a new registration submitted on this form, the following material must accompany the application:

1. Certification with Respect to Citation of Data (EPA Form 8570-29). [If not exempted by 40 CFR 152.81 (b) (4)];
2. Confidential Statement of Formula (EPA Form 8570-4);
3. Formulator's Exemption Statement (EPA Form 8570-27);
4. Five copies of draft labeling;
5. Three copies of any data submitted;
6. Authorization letter where applicable;
7. Matrices where applicable.

Submission of Labeling - Labeling should first be submitted in the form of draft labels with all applications for new registration. Such draft labels may be in the form of typed label text on 8.5 x 11 inch paper for submission or a mockup of the proposed label. If prepared for mockup, it should be constructed in a way as to facilitate storage in an 8.5 x 11 inch file. Mockup labels significantly smaller than 8.5 x 11 inches should be mounted on 8.5 x 11 inch paper for submission.

Submission of Data - Data submitted in support of this application must be submitted in accordance with PR Notice 86-5.

SPECIFIC INSTRUCTIONS: Please read the instructions listed below before completing this application. First determine the type of registration action, listed in Block A, for which you are submitting this application. For applications submitted in connection with New Registration actions, Sections I, III, and IV must be completed by the applicant. For applications submitted in connection with amended reregistration actions, resubmissions, notifications, reregistrations, etc., Sections I, II, and IV must be completed by the applicant.

Block A - Check the appropriate action for which you are submitting this form.

SECTION I - This section must be completed, as applicable, for all registration actions.

1. **Company/Product Number** - Insert your Company Number, if one has been assigned by EPA. This number may have been assigned to you as a basic registrant, a distributor, or as an establishment. If your product is registered, insert the Product Number.
2. **EPA Product Manager** - If known, fill in the name and PM number of the EPA Product Manager.
3. **Proposed Classification** - Specify the proposed classification of this product.
4. **Product Name** - Enter the complete product name of this pesticide as it will appear on the label. The name must be specific to this product only. Duplication of names is not permitted among products of the same company. Do not include any brand name or company line designations.
5. **Name and Address of Applicant** - The name of the firm or person and address shown in your application is the person or firm to whom the registration will be issued. If you are acting in behalf of another party, you must submit authorization from that party to act for them in registration matters. An applicant not residing in the United States must have an authorized agent residing in the United States to act for them in all registration matters. The name and complete mailing address of such an agent must accompany this application.
6. **Expedited Review** - FIFRA section 3 (c) 3 (B) provides for expedited review of applications for registration, or amendments to existing registrations, that are similar or identical to other pesticide products that are currently registered with the EPA. In order for your application to be eligible for expedited review, you must provide us with the EPA Registration Number and product name of the product you believe is similar to or identical to your product. The product must be similar or identical in both formulation and labeled uses.

SECTION II - This section must be completed for all applications submitted to amend the registration only of a currently registered product (Amendment), for a resubmission in response to an Agency letter, for notifications to the Agency, for the submission of final printed labeling, for reregistration and for any other action that pertains to a specific EPA-registered product. This section is not to be used for a new application for registration.

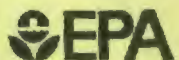
1. **Subject of submission** - Check the applicable block and provide the Agency letter date if appropriate. Provide a brief explanation of the purpose(s) for the submission, such as "the addition of a site, pest or crop (specify)"; "amend the Confidential Statement of Formula by..."; "reregistration submission"; "general label revision of use directions." Attach a separate page if additional space is needed.

SECTION III (Packaging and Container Information) - This Section must be completed for all applications submitted in connection with new registration or applicable amendments.

1. **Type of Packaging** - Check the appropriate block if your product will be packaged in the indicated packaging types. Indicate the size of the individual packets and number per retail container.
2. **Type of Retail Container** - Indicate type of container in which product will be marketed.
3. **Location of Net Contents** - Indicate the location of the net contents information for your product.
4. **Size(s) of Retail Container** - Specify the net contents of all retail containers for your product.
5. **Location of Use Directions** - Indicate the location of the use directions for your product.
6. **Manner in which label is affixed to product** - Indicate the method product label is attached to retail container.

SECTION IV (Contact Point) - This Section must be completed for all applications for Registration actions, i.e., new products registration, resubmission, "me-too," reregistration, etc.

- 1-5. Self-explanatory.
6. EPA Use Only.



United States
Environmental Protection Agency
Washington, DC 20460

☐ Registration
☐ Amendment
☐ Other

OPP Identifier Number

286563

Application for Pesticide - Section I

| | | |
|--|--|---|
| 1. Company/Product Number | 2. EPA Product Manager <i>09</i> | 3. Proposed Classification <input type="checkbox"/> None <input type="checkbox"/> Restricted |
| 4. Company/Product (Name) | PM# | |
| 5. Name and Address of Applicant (Include ZIP Code) <input type="checkbox"/> Check if this is a new address | 6. Expedited Review. In accordance with FIFRA Section 3(c)(3) (b)(i), my product is similar or identical in composition and labeling to: EPA Reg. No. _____ Product Name _____ | |

Section - II

| | |
|--|--|
| <input type="checkbox"/> Amendment - Explain below. | <input type="checkbox"/> Final printed labels in response to Agency letter dated _____ |
| <input type="checkbox"/> Resubmission in response to Agency letter dated _____ | <input type="checkbox"/> "Me Too" Application. |
| <input type="checkbox"/> Notification - Explain below. | <input type="checkbox"/> Other - Explain below. |

Explanation: Use additional page(s) if necessary. (For section I and Section II.)

Section - III

| | | | | | |
|---|---|--|--|---|--|
| 1. Material This Product Will Be Packaged In: | | | | 2. Type of Container | |
| Child-Resistant Packaging <input type="checkbox"/> Yes <input type="checkbox"/> No | Unit Packaging <input type="checkbox"/> Yes <input type="checkbox"/> No | Water Soluble Packaging <input type="checkbox"/> Yes <input type="checkbox"/> No | <input type="checkbox"/> Metal <input type="checkbox"/> Plastic <input type="checkbox"/> Glass <input type="checkbox"/> Paper <input type="checkbox"/> Other (Specify) _____ | | |
| Certification must submitted If "Yes" Unit Packaging wgt. _____ No. per container _____ | | If "Yes" Package wgt. _____ No. per container _____ | | | |
| 3. Location of Net Contents Information <input type="checkbox"/> Label <input type="checkbox"/> Container | | 4. Size(s) Retail Container | | 5. Location of Label Directions <input type="checkbox"/> On Label <input type="checkbox"/> On Labeling accompanying product | |
| 6. Manner in Which Label is Affixed to Product <input type="checkbox"/> Lithograph <input type="checkbox"/> Paper glued <input type="checkbox"/> Stenciled | | <input type="checkbox"/> Other _____ | | | |

Section - IV

| | | | | | |
|---|--|----------|--|-----------------------------------|--|
| 1. Contact Point (Complete items directly below for identification of individual to be contacted, if necessary, to process this application.) | | | | | |
| Name | | Title | | Telephone No. (Include Area Code) | |
| Certification I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law. | | | | | 6. Date Application Received (Stamped) |
| 2. Signature | | 3. Title | | | |
| 4. Typed Name | | 5. Date | | | |

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2. Confidential Statement of Formula (EPA Form 8570-4);
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4. Five copies of draft labeling;
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2. **EPA Product Manager** - If known, fill in the name and PM number of the EPA Product Manager.
3. **Proposed Classification** - Specify the proposed classification of this product.
4. **Product Name** - Enter the complete product name of this pesticide as it will appear on the label. The name must be specific to this product only. Duplication of names is not permitted among products of the same company. Do not include any brand name or company line designations.
5. **Name and Address of Applicant** - The name of the firm or person and address shown in your application is the person or firm to whom the registration will be issued. If you are acting in behalf of another party, you must submit authorization from that party to act for them in registration matters. An applicant not residing in the United States must have an authorized agent residing in the United States to act for them in all registration matters. The name and complete mailing address of such an agent must accompany this application.
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1. **Subject of submission** - Check the applicable block and provide the Agency letter date if appropriate. Provide a brief explanation of the purpose(s) for the submission, such as "the addition of a site, pest or crop (specify)"; "amend the Confidential Statement of Formula by..."; "reregistration submission"; "general label revision of use directions." Attach a separate page if additional space is needed.

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- 1-5. Self-explanatory.
6. EPA Use Only.

Review copy

Emamectin Benzoate Technical

An insecticide for formulation into end-use insecticide products intended for non-domestic food, feed, & outdoor use – head & stem Brassica vegetables, celery & head lettuce

Active Ingredient:

Emamectin Benzoate (CAS No. 137512-74-4) 97.0%

Other Ingredients: 3.0%

Total: 100.0%

Product of Switzerland

EPA Reg. No. 100-902

EPA Est.

Lot# _____

Net Weight: _____

Physical _____ kg

Assay _____ kg

Drum No. _____

KEEP OUT OF REACH OF CHILDREN

SKULL & CROSSBONES]

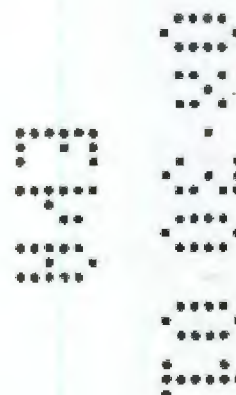
DANGER/PELIGRO

[SKULL & CROSSBONES]

POISON

[red type]

Si usted no entiende la etiqueta, busque a alguien para que se la explique a usted en detalle. (If you do not understand the label find someone to explain it to you in detail.)



PRECAUTIONARY STATEMENTS

Hazards to Humans and Domestic Animals

Corrosive. Causes irreversible eye damage. Do not in eyes or on clothing. Wear protective eyewear (goggles, face shield, or safety glasses) May be fatal if swallowed. Wash thoroughly with soap and water after handling and before eating, drinking, or using tobacco. Remove and wash contaminated clothing before reuse.

Have the product container or label with you when calling a poison control center or doctor or going for treatment.

| FIRST AID | |
|---|---|
| If in eyes | <ul style="list-style-type: none">• Hold eye open and rinse slowly and gently with water for 15-20 minutes.• Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye.• Call a poison control center or doctor for treatment advice |
| If on skin or clothing | <ul style="list-style-type: none">• Take off contaminated clothing.• Rinse skin immediately with plenty of water for 15-20 minutes• Call a poison control center or doctor for treatment advice. |
| If Inhaled | <ul style="list-style-type: none">• Move person to fresh air• If person is not breathing, call 911 or an ambulance, and then give artificial respiration, preferably mouth-to-mouth, if possible.• Call a poison control center or doctor for treatment advice |
| If swallowed | <ul style="list-style-type: none">• Call a poison control center or doctor immediately for treatment advice• Have a person sip a glass of water if able to swallow• Do not induce vomiting unless told to do so by a poison control center or doctor.• Do not give anything by mouth to an unconscious person. |
| HOT LINE NUMBER | |
| In the event of a major fire, spill, or other emergency call 1-800-888-8372 day or night. | |

NOTE TO PHYSICIAN

Recommendations for Medical Treatment for Emamectin Benzoate Acute Toxicity: Early signs of intoxication include mydriasis (dilated pupils), ataxia (unsteadiness), and muscle tremors. Toxicity following accidental ingestion of the concentrate can be minimized by inducing vomiting within ½ hour of exposure. If toxicity from exposure has progressed to cause severe vomiting, the extent of resultant fluid and electrolyte imbalance should be gauged. Appropriate supportive parenteral fluid replacement therapy should be given, along with other required supportive measures (such as maintenance of blood pressure levels) as indicated by clinical signs, symptoms, and measurements. In severe cases, observations should continue for at least several days until clinical condition is stable and normal. Since emamectin benzoate is believed to enhance GABA activity in animals, it is probably wise to avoid drugs that enhance GABA activity (barbiturates, benzodiazepines, valproic acid) in patients with potentially toxic emamectin benzoate exposure. For 24 emergency medical information, call Syngenta Crop Protection, Inc. at 1-800-888-8372.

Environmental Hazards

This pesticide is toxic to fish, birds, mammals, and aquatic invertebrates. Do not discharge effluent containing this active ingredient into lakes, streams, ponds, estuaries, oceans, or other public waters, unless in accordance with the requirements of a National Pollutant Discharge Elimination System (NPDES) permit, and the permitting authority has been notified in writing prior to discharge. Do not discharge effluent containing this product **into** sewer systems without previously notifying the local sewage treatment plant authority. For guidance, contact your State Water Board or Regional Office of the EPA.

[removed bee stnt] ? — ok only for outdoor products

CONDITIONS OF SALE AND LIMITATION OF WARRANTY AND LIABILITY

NOTICE: Read the entire Directions for Use and Conditions of Sale and Limitation of Warranty and Liability before buying or using this product. If the terms are not acceptable, return the product at once, unopened, and the purchase price will be refunded.

The Directions for Use of this product should be followed carefully. It is impossible to eliminate all risks inherently associated with the use of this product. Crop injury, ineffectiveness or other unintended consequences may result because of such factors as manner of use or application, weather or crop conditions, presence of other materials or other influencing factors in the use of the product, which are beyond the control of SYNGENTA CROP PROTECTION, Inc. or Seller. All such risks shall be assumed by Buyer and User, and Buyer and User agree to hold SYNGENTA and Seller harmless for any claims relating to such factors.

SYNGENTA warrants that this product conforms to the chemical description on the label and is reasonably fit for the purposes stated in the Directions for Use, subject to the inherent risks referred to above, when used in accordance with directions under normal use conditions. This warranty does not extend to the use of the product contrary to label instructions, or under abnormal conditions or under conditions not reasonably foreseeable to or beyond the control of Seller or SYNGENTA, and Buyer and User assume the risk of any such use. SYNGENTA MAKES NO WARRANTIES OF MERCHANTABILITY OR OF FITNESS FOR A PARTICULAR PURPOSE NOR ANY OTHER EXPRESS OR IMPLIED WARRANTY EXCEPT AS STATED ABOVE.

In no event shall SYNGENTA or Seller be liable for any incidental, consequential or special damages resulting from the use or handling of this product. **THE EXCLUSIVE REMEDY OF THE USER OR BUYER, AND THE EXCLUSIVE LIABILITY OF SYNGENTA AND SELLER FOR ANY AND ALL CLAIMS, LOSSES, INJURIES OR DAMAGES (INCLUDING CLAIMS BASED ON BREACH OF WARRANTY, CONTRACT, NEGLIGENCE, TORT, STRICT LIABILITY OR OTHERWISE) RESULTING FROM THE USE OR HANDLING OF THIS PRODUCT, SHALL BE THE RETURN OF THE PURCHASE PRICE OF THE PRODUCT OR, AT THE ELECTION OF SYNGENTA OR SELLER, THE REPLACEMENT OF THE PRODUCT.**

SYNGENTA and Seller offer this product, and Buyer and User accept it, subject to the foregoing conditions of sale and limitations of warranty and of liability, which may not be modified except by written agreement signed by a duly authorized representative of SYNGENTA.

DIRECTIONS FOR USE

It is a violation of Federal law to use this product in a manner inconsistent with its labeling.

This product may be used only to manufacture/formulate other insecticide products registered and labeled for use on head and stem Brassica vegetables, celery, and head lettuce.

STORAGE AND DISPOSAL

Do not store near food or feed. Do not contaminate water, food, or feed by storage or disposal.

Store in a tightly closed original container in a cool, dry place.

Pesticide Disposal

Pesticide wastes are acutely hazardous. Improper disposal of excess pesticide, or rinsate is a violation of Federal law. If these wastes cannot be disposed of by use according to label instructions, contact your State Pesticide or Environmental Control Agency, or the Hazardous Waste representative at the nearest EPA Regional Office for guidance. Pesticide that cannot be used or chemically reprocessed must be disposed of according to federal, state, or local procedures under the Resource Conservation and Recovery Act.

} RCRA?
OK

Container Disposal

Bulk

Thoroughly clean container before reuse. Consult federal, state, or local disposal authorities for approved alternative procedures.

250 Gal Mini Bulk

This is a refillable container that must be returned to an authorized Syngenta refilling facility for refilling or disposal.

Other Containers

Triple rinse (or equivalent). Then offer for recycling or reconditioning, or puncture and dispose of in a sanitary landfill, or by other procedures approved by state and local authorities.

Note: For minor spills, leaks, etc. follow all precautions indicated on this label and clean up immediately. Take special care to avoid contamination of equipment and facilities during cleanup procedures and disposal of wastes. In the event of a major spill, fire, or other emergency, call 1-800-888-8372, day or night.

| |
|---|
| For non-emergency (e.g. current product information) call Syngenta Crop Protection, Inc. at 1-800-334-9481 |
|---|

©2001 Syngenta

Syngenta Crop Protection, Inc.
Greensboro, North Carolina 27409

SCP

August 30, 2001 –draft revised label to EPA, revised first aid statements according to PR Notice 2000-3, revised ingredient statement according to new CSF and prod. chem, revised and added storage and disposal statements, specified on front panel end-use product uses supported for this active ingredient. Corrected label by adding Spanish signal word and warning statement, deleted chemical name of active – common name and CAS no. are sufficient, changed all references to Novartis to Syngenta and replaced Warranty statement with new Syngenta Warranty Statement, changed country of origin to Switzerland, revised ingredient statement per PR Notices 97-5 & 97-6

CBB – 8/29/01


 Thomas Harris

08/23/2001 05:31 PM

To: carolyn.brinkley@syngenta.com

cc: johnny.reynolds@syngenta.com, Linda

Kutney/DC/USEPA/US@EPA, john.hott@syngenta.com

Subject: emamectin CSF 

The purpose of this email is to summarize our phone conversations today.

To resolve the issues addressed in the 8/22/01 rejection letter Syngenta will:

1) raise the "other" item on the CSF by 0.1 so the numbers total 100%

2) label - Whether the "related compounds" goes up top with the "active ingredients" or is buried within the "other ingredients" depends on whether the registrant claims the related compounds have any pesticidal activity. It has to be proven that the pesticidal activity exists to get the related compounds up top with the a.i.; the default is to include them with the other ingredients if you don't know if there is pesticidal activity or not. Since both avermectin and emamectin technicals included the related compounds with the a.i. when originally registered I suspect that there was some discussion of their pesticidal activity (along with efficacy data to support the claim). I would therefore ask that if you want to change this and bury them in the other ingredients that you provide a compelling argument as to why. If you bury the related compounds on emamectin you will probably also need to change the avermectin technical label and CSF.

EITHER: Keep format as on current but update numbers, i.e. (verify my #'s below)

| | |
|------------------------|------|
| active ingredients | |
| emamectin benzoate ... | 97.0 |
| related compounds | 1.9 |
| other ingredients | 1.1 |

OR: Provide justification that the related compounds have no pesticidal activity. Label can then state:

| | |
|------------------------|------|
| active ingredients | |
| emamectin benzoate ... | 97.0 |
| other ingredients | 3.0 |

Please give me a phone call to let me know which way you'll proceed on the label before you send it in. My goal is to work out the kinks ahead of time so the paperwork is perfect when submitted and can be quickly accepted. Thanks.

Tom Harris
EPA/OPPTS/OPP/RD/IRB
(703) 308-9423
harris.thomas@epa.gov



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

AUG 21 2001

Carolyn Brinkley
Syngenta Crop Protection, Inc.
PO Box 18300
Greensboro, NC 27419

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

re: Eamectin Benzoate Technical, EPA Reg. # 100-902
revised basic CSF and new product chemistry submitted 5/18/01
REJECTED

Dear Ms. Brinkley:

The Agency has reviewed your submission for a revised Confidential Statement of Formula (CSF). The Agency has also reviewed new product chemistry data (MRID 454208-01). The Confidential Statement of Formula dated 5/01/01 for the **basic** formulation is **NOT ACCEPTABLE**.

Attached please find a copy of the product chemistry review by Linda Kutney dated 8/17/01. The review details several issues that need to be resolved. In general, you must:

- 1) Resolve several CSF issues (percentage of various ingredients, identification of impurities if $>0.1\%$). *Note: Part of the confusion with the percentages may deal with the last two ingredients on the CSF. Are these inerts or impurities? Compare to your currently accepted CSF.*
- 2) Submit a revised product label if the ingredient percentages differ from the currently registered label.

In addition, please submit a separate CSF for each producer of the product (two are listed on the basic CSF dated 5/1/01). If your intent is to phase out the original producer and switch to a new producer then I suggest you make the new producer the basic CSF while the original producer is alternate #1 CSF. If you eventually stop using the original producer you can then correct the current CSFs by simply telling EPA to drop the alternate #1 CSF (i.e. you only submit a letter, not a revised basic CSF). If you plan to continue using both producers then it does not matter which is listed on which CSF but you should still submit a basic and alternate #1 to account for each producer separately.

If you have any questions please contact me at (703) 308-9423 or harris.thomas@epa.gov.

Yours truly,

Thomas C. Harris, Biologist
Insecticide-Rodenticide Branch
Registration Division (7505C)

enclosure

Internet Address (URL) • <http://www.epa.gov>

Recycled/Recyclable • Printed with Vegetable Oil Based Inks on Recycled Paper (Minimum 30% Postconsumer)

DP BARCODE: D276416

#12313

CASE: 046738
SUBMISSION: S600553

DATA PACKAGE RECORD
BEAN SHEET

DATE: 07/23/01
Page 1 of 1

*** CASE/SUBMISSION INFORMATION ***

CASE TYPE: REGISTRATION ACTION: 345 TECH-FORMULA CHANGE AMND
RANKING : 5 POINTS ()
CHEMICALS: 122806 4''-Epimethylamino-4''-deoxyavermectin B1a and B1b 95.0000%
ID#: 000100-00902 EMAMECTIN BENZOATE TECHNICAL
COMPANY: 000100 SYNGENTA CROP PROTECTION, INC.
PRODUCT MANAGER: 04 MEREDITH LAWS 703-308-9366 ROOM: CM2 282
PM TEAM REVIEWER: THOMAS HARRIS 703-308-9423 ROOM: CM2 211
RECEIVED DATE: 05/25/01 DUE OUT DATE: 08/23/01

*** DATA PACKAGE INFORMATION ***

DP BARCODE: 276416 EXPEDITE: N DATE SENT: 07/23/01 DATE RET.: / /
CHEMICAL: 122806 4''-Epimethylamino-4''-deoxyavermectin B1a and B1b benzoate
DP TYPE: 001

| | CSF: Y | | LABEL: Y | |
|---------------|---------|----|----------|-----|
| ASSIGNED TO | DATE | IN | DATE | OUT |
| DIV : RD | / | / | / | / |
| BRAN: TRB | / | / | / | / |
| SECT: CHEM | / | / | / | / |
| REVR : Kurney | 8/10/01 | | / | / |
| CONTR: | / | / | / | / |

ADMIN DUE DATE: 8/20/01
NEGOT DATE: 09/06/01
PROJ DATE: / /

*** DATA REVIEW INSTRUCTIONS ***

MRID 454208-01

Please review new product chemistry, analytical method, and resulting revised CSF. Same manufacturer, just redid studies and results are different. Note change in nominal a.i. (they did not send label; I will ask for it).

I've included a copy of current accepted CSF along with reviews that went into accepting it.

-Tom Harris
RD/IRB
308-9423
rm 213

*** DATA PACKAGE EVALUATION ***

No evaluation is written for this data package

*** ADDITIONAL DATA PACKAGES FOR THIS SUBMISSION ***

| DP BC | BRANCH/SECTION | DATE OUT | DUE BACK | INS | CSF | LABEL |
|-------|----------------|----------|----------|-----|-----|-------|
|-------|----------------|----------|----------|-----|-----|-------|

96.0
3.0

97.0
2.9

inerts 0.1



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

OPPTS/OPP/RD/TRB/PRODUCT CHEMISTRY TEAM

WASHINGTON, D.C. 20460

DATE: 17/AUG/2001

SUBJECT: PRODUCT CHEMISTRY REVIEW OF MP ☐ EP ☐ TECHNICAL ☒

DP BARCODE No.: D276416

REG./File Symbol: 100-902

PRODUCT NAME: Emamectin Benzoate Technical (MK-244)

COMPANY: Syngenta Crop Protection, Inc.

FROM: Linda L. Kutney, Chemist
Product Chemistry Team
Technical Review Branch/RD (7505C)

Linda L. Kutney
8/17/01

TO: Deborah McCall, Thomas Harris PM 4
Insecticide Rodenticide Branch/RD(7505C)

prod chem

Syngenta Crop Protection, Inc., in a letter dated 5/18/01, has submitted data intended to support registration of their product "Technical Emamectin Benzoate," also referred to as MK-244 of Avermectin, Reg. No. 100-902, containing a nominal concentration of 97.0% Emamectin Benzoate. The product was previously registered by Merck and has been transferred to Syngenta, who will be producing it in the future. New product chemistry data, new analytical methods and a new CSF was submitted, with MRID Nos. 454208-01. A basic proposed CSF, dated 5/1/01 was also submitted.

The reviewer contacted Carolyn Brinkley of Syngenta (336-632-2838) on 8/14/01 to request a copy of the new label for the technical Emamectin Benzoate, to give details about the amount of impurities in the CSF, and to ask if any additional Group B data had been submitted. Syngenta responded on 8/15/01 by confirming that no new Group B data were submitted for physical chemical properties and these are not expected to be different from the values reported earlier. Syngenta also explained that the impurities in their CSF total 2.9% by weight of the total percentage of the technical Emamectin Benzoate, not 3.0%. Syngenta did not confirm the previous commitment to Fax the Agency a revised label by 8/16/01.

Previous Agency conclusions regarding physical chemical properties are summarized in this review. Reviews consulted included the following: 5/4/94 review by Mike Flood (MRID Nos 427436-44 to -51, 427942-02, 428515-20 to -22, -25 and 428689-03 to -04); 7/9/93 Al Smith review (MRID Nos 427436-44 to -51); and the 11/30/00 Bruce Kitchens review (MRID Nos 448837-01 to -05).

FINDINGS

- The densities, pH's, and flash points/flame extensions on the proposed 5/1/01 CSF for Technical Eamectin Benzoate are identical to values on the previously accepted 5/18/99 CSF for Technical Eamectin Benzoate.
- The Physical or Chemical Hazard statements on the proposed label for Eamectin Benzoate are appropriate with respect to its flammability and satisfy the requirements specified in 40 CFR 156.10 (h)(2)(iii).
- The proposed storage and disposal instructions satisfy the requirements of PR 83-3.
- The beginning materials and production process data requirements satisfy Guideline 830.1600 and 830.1620 (See MRID No. 454208-01).
- The discussion of formation of impurities, Guideline 830.1670, is acceptable. (See MRID No. 454208-01)
- The Guideline requirement for preliminary analysis, Guideline 830.1700, is acceptable. (See Confidential Appendix)
- The analytical method requirement for the Eamectin Benzoate ai (40 CFR 158.180) is satisfied. A summary of this method is attached in the Appendix.

CONCLUSIONS:

TRB has reviewed this submission and concluded that it could recommend for registration, providing that Syngenta adequately addresses deficiencies *italicized* below:

- *The nominal concentration of the Eamectin Benzoate a.i. on the proposed 5/1/01 CSF does not agree with the label concentration, in accordance with the requirements of PR 91-2.*
- *The label statement concerning process related impurities and inert ingredients is not consistent with the CSF. The label must be revised.*
- *All impurities present at levels of 0.1% or greater must be identified on the CSF.*
- *Syngenta must update their label to reflect the fact that they are replacing Merck as the*

Registrant.

- *Syngenta must ensure that the sum of all of the components in the CSF, % by weight, in column 13b, total 100.0%.*
- *Column 11 of the proposed 5/1/01 CSF should give the full supplier name and street address for all components in the label, except for the impurities [REDACTED]*
- *Guideline 830.1550, product identity and composition requirements are not acceptable, but may be satisfied by addressing the deficiencies concerning the CSF and label.*
- *Guideline 830.1600 (Beginning Materials), Guideline 830.1650 (Formulation Process) and Guideline 830.1670 (Formation of Impurities) were adequately provided in MRID 454208-01*
- *The requirement for Preliminary Analysis, Guideline 830.1700 is adequately satisfied.*
- *Guideline 830.1750, certified limits, is not satisfied because impurities present over 0.1% must all be listed on the CSF. The total of all values for %-by-weight in column 13b must be 100.0%. The certified limits for Emamectin Benzoate ai are slightly wider than the standard limits specified in, but are acceptable.*
- *Group B data requirements are satisfied; and, the physical chemical properties were previously reported in various Agency reviews, referenced here and summarized in this report.*
- *Guideline 830.1900, Submittal of Samples, is required for integrated products and for those of toxicological concern, as well as for nonintegrated products with interference or method problems, etc. A sample of the tga will be required prior to its registration.*

SUBJECT: PRODUCT CHEMISTRY REVIEW OF MP ☐ EP ☐ TECHNICAL ☒

DP BARCODE No.: D276416

REG./File Symbol: 100-902

PRODUCT NAME: Emamectin Benzoate Technical (MK-244)

COMPANY: Syngenta Crop Protection, Inc.

1. Reviewer: Linda L. Kutney
2. Company: Syngenta Crop Protection, Inc.
3. Type of Submission: Registration ☒ Reregistration ☐ New ☐ Resubmission ☐
Amendment ☐ "ME-TOO" ☐ Alternate Formulation ☐ Experimental Use
Permit ☐ Other (Specify) ☒ TECHNICAL
4. If "Me-TOO" Registration, this product is ☒ is not ☐ similar or substantially similar
to EPA's Reg. No.:

CONFIDENTIAL STATEMENT OF FORMULA

5. Type of formulation and the sources of active ingredients:
 - Non-integrated formulation system.....☐
 - Arc all technical grade active ingredients used registered? ● yes ☐ ● no ☐ , If no,
specify The technical is under process of registration
 - Integrated formulation system.....☒
6. Clearance of intentionally added ingredients in the formulation for the intended use
(indicate in the Confidential Appendix those that are not cleared; the PC Codes should be
provided by the chemist on the CSF for those that are cleared):
- 6(a) Formulation intended for food use under 40CFR§180.1001:
 - yes ☐ ● no ☐ ● Some are cleared, others are not ☐
 - LABEL STATES TECHNICAL IS INTENDED FOR FORMULATION USE ONLY
 - Cleared under list: ● c ☐ ● d ☐ ● e ☐ Are there any limitations for use as an
inert under 40CFR§180.1001?
 - yes ☐ ● no ☐ , If yes, specify
 - Not Applicable
- 6(b) Formulation intended for non-food use:
 - yes ☐ ● no ☐ ● Some are cleared, others are not ☐
 - LABEL STATES TECHNICAL IS INTENDED FOR FORMULATION USE ONLY

- 6(c) Clearance by the FDA of certain formulations under 21CFR§170 to 199. Examples: (a) indirect food additives, such as food contact surface sanitizers; adhesives, coatings, paper and paperboard products that may contact food in packaging or holding; and (b) substances generally recognized as safe (GRAS).

• yes ☐ • no ☐ • Some are cleared, others are not ☐

7. The density, pH, and flammability values given on the CSF are identical with those of GRN 830.7300(density), 830.7000(pH), and 830.6315(Flammability), respectively:

• yes ☒ • no ☐

These value, reported on the proposed 5/1/01 CSF, are identical to the values registered 5/18/99, in the previously accepted CSF.

8. The nominal concentrations (NC) of the active ingredients and the upper and lower certified limits (UCL & LCL) are as follows:

| Active ingredient(s) | NC | % by weight | |
|--|------|-------------|------|
| | | UCL | LCL |
| Enamectin Benzoate Technical, 97.0% Reg No 100-902 | 97.0 | 100 | 95.0 |

9. The calculated NCs, based on the pure active ingredients (PAI), are identical to those on the label:

• yes ☐ • no ☒

No, Label accepted 5/24/99 says only 96.0%, not 97.0% A revised label is needed.

10. The certified limits are within the standard limits as per 40CFR§158.175 or are adequately explained if different: • yes ☒ • no ☐

Certified limits are acceptable.

PRODUCT LABEL

A revised label is needed.

11. The chemical names of the active ingredients on the label are identical to those on the CSF: • yes ☒ • no ☐

12. The appropriate physical and chemical hazards statement regarding flammability or explosive characteristics of the product are given on the label:

• yes ☐ • no ☐ • not applicable ☒

Material is a solid

13. The storage and disposal instructions for the pesticide and container are in compliance with PR Notice 84-1 for household use products or PR Notice 83-3 for all other uses:

• yes ☒ • no ☐

PRODUCT CHEMISTRY DATA (SERIES 830 Subgroup A & Subgroup B)

| 14. Chemical IDs/Manufacture/ Analytical Information New Guideline:830.-- | Data Fulfilled | MRID No. |
|--|--|-----------------------------------|
| 1550. Chemical Identity(CSF) | <i>No, Impurities present over 0.1% must all be listed on the CSF, Total % by weight in column 13b must be 100.0%</i> | 454208-01 CSF |
| 1600. Beginning Materials 1650. Formulation Process | Yes Yes | 454208-01 CSF |
| 1670. Impurity Formation | Yes | 454208-01 |
| 1700. Preliminary Analysis 1750. Certified Limits (CSF) | Yes <i>No, Impurities present over 0.1% must all be listed on the CSF, Total % by weight in column 13b must be 100.0%</i> | 454208-01 454208-01 CSF |
| 1800. Enforcement of Analytical Method (required for integrated products & those of tox. concern) | Yes | 454208-01 |
| 1900. Submittal of Samples (required for integrated products, those of tox. concern, and for nonintegrated products with interference, etc, method problems) | <i>No, this will be required for the integrated tgai, which is of toxicological concern</i> | |

| <u>15. Physical/Chemical Properties</u> <u>New Guideline No. 830.---</u> | <u>Data Ful-filled</u> | <u>Value or Qualitat. Descrip.</u> | <u>MRID No.</u> |
|---|------------------------|---|------------------|
| 6302. Color (if required by PR 92-5) | Yes | off white, white | 427436-46 to -51 |
| 6303. Physical State | Yes | Solid | 427436-46 to -51 |
| 6304. Odor (if required by PR 92-5) | Yes | not tested | 427436-46 to -51 |
| 6305. Melting Point | N/A | | 427436-46 to -51 |
| 6306. Boiling Point | N/A | | 427436-46 to -51 |
| 7300. Density | Yes | 1.20 g/cc Also, 74.9 lb/ft 3 on 5/1/01 CSF | 427436-46 to -51 |
| 7840, 7860. Solubility | Yes | 105 mg/l in pH5 water. 101 mg/l in pH 5 buffer. 93 mg/l in pH7 buffer Not detected in pH 9 buffer. | 448837-04 |
| 7950. Vapor Pressure | N/A | 2-4 x 10 (-8) Torr | 427436-46 to -51 |
| 7370. Dissociation Constant | N/A | 4.2 Benzoic Acid 7.6 "methyl-amino" | 427436-46 to -51 |
| 7550,7560,7570. Octanol Water Partition Coefficient (Log P) | Yes | 5.7 for the B1a component 5.2 for the B1b minor component | 448837-03 |

| | | | |
|------------------------------------|-----|--|------------------|
| 7000. pH | Yes | Reported to be 6.4 for 1% aq. suspension @ 25C, but given as 6.7 @25 C, 1% aq solution, on 5/1/01CSF | 448837-02 CSF |
| 6317. Stability | N/A | > 1 Year | 427436-46 to -51 |
| 6314. Oxidation Reduction Reaction | Yes | | 427436-46 to -51 |
| 6315. Flammability/Flame Extension | Yes | | 427436-46 to -51 |
| 6316. Explodability | Yes | | 427436-46 to -51 |
| 6317. Storage Stability | Yes | | 427436-46 to -51 |
| 7100. Viscosity | N/A | | 427436-46 to -51 |
| 6319. Miscibility | N/A | Solid | 427436-46 to -51 |
| 6320. Corrosion Characteristics | Yes | | 427436-46 to -51 |
| 6321. Dielectric Breakdown Voltage | N/A | | 427436-46 to -51 |
| 7100. Viscosity | N/A | | 427436-46 to -51 |
| 7300. Density/Bulk Den. | Yes | | 427436-46 to -51 |
| MISC Henry's Law Constant | Yes | 3.80×10^{-10} atm-m ³ /mole | 448837-05 |
| | | | |

NA = Not Applicable;

APPENDIX

Method AW-212/1, brief summary

The test material is weighed accurately, included in a 100 ml volumetric flask with MK 244 reference substance, acetonitrile and trifluoroacetic acid, and sonicated for 5 minutes. The Response Factor and % purity of Emamectin Benzoate is calculated using the peak area of the sample relative to the reference, the purity and weight of the sample and reference, and other specific factors specific to the test and reference solutions used.

The IR spectra of the sample is qualitatively compared with the reference spectrum, using 1 mg of sample in 100 mg of a Potassium Bromide pellet. This method is a liquid chromatographic (LC) analysis which separates and quantitates Emamectin Benzoate B1a and B1b, as well as the process related impurities. Accuracy, recovery and precision of the method were acceptable. The LC conditions are as follows:

| | |
|----------------------------|--|
| Detector | 10 mm thick, 245 nm (UV detector), IV MerckLaChrom L 7400 |
| Column | Kromasil 100 C8, 3.5 micro-m particle size, 250 mm length, |
| Column Temperature | room temperature |
| Sample size | 10 micro-l of reference |
| Flow rate | 1.0 ml/minute |
| Duration of Chromatography | 74 minutes |

At the conditions of testing, the Emamectin Benzoate B1a (NOA 426007) peak appears at 44.3 minutes and the Emamectin Benzoate B1b(NOA-422390) peak appears approximately at 33.8 minutes.

$$\% \text{ Emamectin Benzoate} = \frac{\text{Emamectin Benzoate B1a (NOA 426007)} + \text{Emamectin Benzoate B1b(NOA-422390)}}{\text{Emamectin Benzoate B1a (NOA 426007)} + \text{Emamectin Benzoate B1b(NOA-422390)}}$$

CONFIDENTIAL APPENDIX

Preliminary Analysis Guideline 830.1700

The preliminary five batch analyses supports the label and CSF claim of 97.0% Enamectin Benzoate.

| | Average | CSF % by Wt |
|------------------------------|---------|-------------|
| Enamectin Benzoate Technical | | 97.0% |
| Enamectin Benzoate B1a | | |
| Enamectin Benzoate B1b | | |

04

This is an ACCEPTED submission.

One copy of the PPC diagnosis and one copy of the annotated bibliography are provided for your files. The PPC has already mailed out the submitter's copy of the data.

This is a PARTIALLY ACCEPTED/COMPLETELY REJECTED submission.

A copy of the PPC diagnosis and the annotated bibliography are provided for your files. A second copy is provided for your use in corresponding with the data submitter.

JUN 12 2001

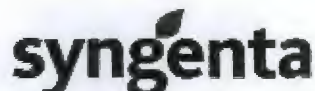
U.S. ENVIRONMENTAL PROTECTION AGENCY
Office of Pesticide Programs

SYNGENTA CROP PROTECTION, INC.
P.O. BOX 18300
GREENSBORO, NC 274198300

Report of Analysis for Compliance with PR Notice 86-5

Thank you for your transmittal of 05/25/01. Our staff has completed a preliminary analysis of the material. The results are provided as follows:

Your submittal was found to be in full compliance with the standards for submission of data contained in PR Notice 86-5. A copy of your bibliography is enclosed, annotated with Master Record ID's (MRIDs) assigned to each document submitted. Please use these numbers in all future references to these documents. Thank you for your cooperation. If you have any questions concerning this data submission, please raise them with the cognizant Product Manager, to whom the data have been released.



Syngenta Crop Protection, Inc Tel 336 632 6000
P.O. Box 18300
Greensboro, NC 27419-8300

454208-00

Carolyn F. Brinkley
Sr. Regulatory Product Manager
Syngenta Crop Protection, Inc
Phone: (336) 632-2838
Fax: (336) 292-6374
E-mail: carolyn.brinkley@syngenta.com

May 18, 2001

Document Processing Desk [AMEND]
Office of Pesticide Programs (7504C)
U.S. Environmental Protection Agency
Ariel Rios Building
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460

Attention: Mr. Thomas Harris
Insecticide-Rodenticide Branch

**SUBJECT: EMAMECTIN BENZOATE TECHNICAL, EPA REG. NO. 100-902
CHANGE IN MANUFACTURER OF ACTIVE INGREDIENT
REVISED CSF & SUPPORTING DATA**

Gentlemen:

Technical emamectin benzoate was previously registered by Merck. The registration has since been transferred to Syngenta Crop Protection and Syngenta will be producing the product in the future. For this reason, Syngenta generated new product chemistry data that include new analytical methods. The enclosed confidential statement of formula is based on these data.

Approval of the revised confidential statement of formula by August is needed to insure that we can meet our upcoming production requirements and your review of this submission will be appreciated. If you have any questions or comments, please contact me. I can be reached at (336) 632-2838.

Sincerely yours,

Carolyn F. Brinkley
Sr. Regulatory Product Manager
Regulatory Affairs

Enclosures: EPA Application for Pesticide Amendment
Volume 1 of 2 - Transmittal Document
Volume 2 of 2 - Manufacturing Process Description and Supporting Data for
Emamectin Benzoate Technical (Product Chemistry Group A
Data)

**VOLUME 1 OF 2 OF SUBMISSION
(TRANSMITTAL DOCUMENT)**

1. NAME AND ADDRESS OF SUBMITTER

SYNGENTA CROP PROTECTION, INC.
P.O. BOX 18300
GREENSBORO, NC 27419

**2. REGULATORY ACTION IN SUPPORT OF WHICH THIS PACKAGE IS
SUBMITTED**

EMAMECTIN BENZOATE TECHNICAL: EPA REG. NO 100-902
NOTIFICATION OF ALTERNATIVE SOURCE OF SUPPLY

3. TRANSMITTAL DATE

05/21/2001

4. LIST OF SUBMITTED STUDIES

| MRID NUMBER | VOLUME NUMBER | STUDY TITLE | EPA GUIDELINE NUMBER |
|----------------|------------------|---|--|
| ADMIN. | 1 OF 2 | TRANSMITTAL DOCUMENT | NOT APPLICABLE |
| 45420801 | 2 OF 2 | MANUFACTURING PROCESS DESCRIPTION AND SUPPORTING DATA FOR EMAMECTIN BENZOATE TECHNICAL; STUDY NO. PC- 01-014; (402) (402836) | 830.1550, 830.1600, 830.1620, 830.1670, 830.1700, 830.1750, 830.1800 |

COMPANY OFFICIAL: CAROLYN F. BRINKLEY
(NAME)

Carolyn Brinkley
(SIGNATURE)

COMPANY NAME: SYNGENTA CROP PROTECTION, INC.

COMPANY CONTACT: CAROLYN F. BRINKLEY
(NAME)

(336) 632-2838
(PHONE)



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

06/05/2001

CAROLYN F. BRINKLEY
SYNGENTA CROP PROTECTION, INC.
P.O. BOX 18300
GREENSBORO NC 274198300

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

PRODUCT NAME: EMAMECIN BENZOATE TECHNICAL
COMPANY NAME: SYNGENTA CROP PROTECTION, INC.
OPP IDENTIFICATION NUMBER: 277150
EPA REGISTRATION NUMBER: 100-902
EPA RECEIPT DATE: 05/25/2001

SUBJECT: RECEIPT OF AMENDMENT

DEAR REGISTRANT:

The Office of Pesticide Programs has received your application for an amendment and it has passed an administrative screen for completeness.

During the initial screen we determined that the application qualifies for fast track review. The package will now be forwarded to the Product Manager for review to determine its acceptability.

If you have any questions, please contact Insecticide Branch, Product Manager 03, at (703) 305-6891.

Sincerely,

A handwritten signature in cursive script, appearing to read "Julie".

Front End Processing Staff
Information Services Branch
Program Management and Support Division

Syngenta Crop Protection, Inc Tel 336 632 6000
P.O. Box 18300
Greensboro, NC 27419-8300

syngenta

454208-00

Carolyn F. Brinkley
Sr. Regulatory Product Manager
Syngenta Crop Protection, Inc
Phone: (336) 632-2838
Fax: (336) 292-2374
E-mail: carolyn.brinkley@syngenta.com

May 18, 2001

Document Processing Desk [AMEND]
Office of Pesticide Programs (7504C)
U.S. Environmental Protection Agency
Ariel Rios Building
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460

Attention: Mr. Thomas Harris
Insecticide-Rodenticide Branch

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CHANGE IN MANUFACTURER OF ACTIVE INGREDIENT
REVISED CSF & SUPPORTING DATA**

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Approval of the revised confidential statement of formula by August is needed to insure that we can meet our upcoming production requirements and your review of this submission will be appreciated. If you have any questions or comments, please contact me. I can be reached at (336) 632-2838.

Sincerely yours,


Carolyn F. Brinkley
Sr. Regulatory Product Manager
Regulatory Affairs

Enclosures: EPA Application for Pesticide Amendment
Volume 1 of 2 – Transmittal Document
Volume 2 of 2 – Manufacturing Process Description and Supporting Data for
Emamectin Benzoate Technical (Product Chemistry Group A
Data)

**VOLUME 1 OF 2 OF SUBMISSION
(TRANSMITTAL DOCUMENT)**

1. NAME AND ADDRESS OF SUBMITTER

SYNGENTA CROP PROTECTION, INC.
P.O. BOX 18300
GREENSBORO, NC 27419

**2. REGULATORY ACTION IN SUPPORT OF WHICH THIS PACKAGE IS
SUBMITTED**

EMAMECTIN BENZOATE TECHNICAL: EPA REG. NO 100-902
NOTIFICATION OF ALTERNATIVE SOURCE OF SUPPLY

3. TRANSMITTAL DATE

05/21/2001

4. LIST OF SUBMITTED STUDIES

| MRID NUMBER | VOLUME NUMBER | STUDY TITLE | EPA GUIDELINE NUMBER |
|----------------|------------------|---|--|
| ADMIN. | 1 OF 2 | TRANSMITTAL DOCUMENT | NOT APPLICABLE |
| 45420801 | 2 OF 2 | MANUFACTURING PROCESS DESCRIPTION AND SUPPORTING DATA FOR EMAMECTIN BENZOATE TECHNICAL; STUDY NO. PC- 01-014; (402) (402836) | 830.1550, 830.1600, 830.1620, 830.1670, 830.1700, 830.1750, 830.1800 |

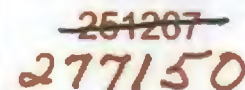
COMPANY OFFICIAL: CAROLYN F. BRINKLEY
(NAME)

Carolyn Brinkley
(SIGNATURE)

COMPANY NAME: SYNGENTA CROP PROTECTION, INC.

COMPANY CONTACT: CAROLYN F. BRINKLEY
(NAME)

(336) 632-2838
(PHONE)



EPA-FRM (G-CA-DOC-REGAFFRS) 2/5/97 - b1

PAPERWORK REDUCTION ACT NOTICE and INSTRUCTIONS

PAPERWORK REDUCTION ACT NOTICE: Public reporting burden for this collection of information is estimated to average 0.85 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding the burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Chief, Information Policy Branch, (2136), U.S. Environmental Protection Agency, 401 M Street, SW, Washington, DC 20460.

INSTRUCTIONS: This form is to be used for all applications for new registration, end use reregistration, amendment, resubmission, to applications for notifications, final printed labeling, reregistration, etc. In order to process an application for a new registration submitted on this form, the following material must accompany the application:

1. Certification with Respect to Citation of Data (EPA Form 8570-29). [If not exempted by 40 CFR 152.81 (b) (4)];
2. Confidential Statement of Formula (EPA Form 8570-4);
3. Formulator's Exemption Statement (EPA Form 8570-27);
4. Five copies of draft labeling;
5. Three copies of any data submitted;
6. Authorization letter where applicable;
7. Matrices where applicable.

Submission of Labeling - Labeling should first be submitted in the form of draft labels with all applications for new registration. Such draft labels may be in the form of typed label text on 8.5 x 11 inch paper for submission or a mockup of the proposed label. If prepared for mockup, it should be constructed in a way as to facilitate storage in an 8.5 x 11 inch file. Mockup labels significantly smaller than 8.5 x 11 inches should be mounted on 8.5 x 11 inch paper for submission.

Submission of Data - Data submitted in support of this application must be submitted in accordance with PR Notice 86-5.

SPECIFIC INSTRUCTIONS: Please read the instructions listed below before completing this application. First determine the type of registration action, listed in Block A, for which you are submitting this application. For applications submitted in connection with New Registration actions, Sections I, III, and IV must be completed by the applicant. For applications submitted in connection with amended reregistration actions, resubmissions, notifications, reregistrations, etc., Sections I, II, and IV must be completed by the applicant.

Block A - Check the appropriate action for which you are submitting this form.

SECTION I - This section must be completed, as applicable, for all registration actions.

1. Company/Product Number - Insert your Company Number, if one has been assigned by EPA. This number may have been assigned to you as a basic registrant, a distributor, or as an establishment. If your product is registered, insert the Product Number.
2. EPA Product Manager - If known, fill in the name and PM number of the EPA Product Manager.
3. Proposed Classification - Specify the proposed classification of this product.
4. Product Name - Enter the complete product name of this pesticide as it will appear on the label. The name must be specific to this product only. Duplication of names is not permitted among products of the same company. Do not include any brand name or company line designations.
5. Name and Address of Applicant - The name of the firm or person and address shown in your application is the person or firm to whom the registration will be issued. If you are acting in behalf of another party, you must submit authorization from that party to act for them in registration matters. An applicant not residing in the United States must have an authorized agent residing in the United States to act for them in all registration matters. The name and complete mailing address of such an agent must accompany this application.
6. Expedited Review - FIFRA section 3 (c) 3 (B) provides for expedited review of applications for registration, or amendments to existing registrations, that are similar or identical to other pesticide products that are currently registered with the EPA. In order for your application to be eligible for expedited review, you must provide us with the EPA Registration Number and product name of the product you believe is similar to or identical to your product. The product must be similar or identical in both formulation and labeled uses.

SECTION II - This section must be completed for all applications submitted to amend the registration only of a currently registered product (Amendment), for a resubmission in response to an Agency letter, for notifications to the Agency, for the submission of final printed labeling, for reregistration and for any other action that pertains to a specific EPA-registered product. This section is not to be used for a new application for registration.

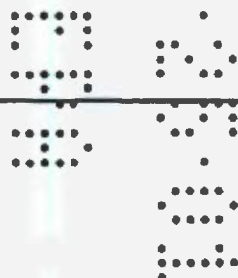
1. Subject of submission - Check the applicable block and provide the Agency letter date if appropriate. Provide a brief explanation of the purpose(s) for the submission, such as "the addition of a site, pest or crop (specify)"; "amend the Confidential Statement of Formula by..."; "reregistration submission"; "general label revision of use directions." Attach a separate page if additional space is needed.

SECTION III - (Packaging and Container Information) - This Section must be completed for all applications submitted in connection with now registration or applicable amendments.

1. Type of Packaging - Check the appropriate block if your product will be packaged in the indicated packaging types. Indicate the size of the individual packets and number per retail container.
2. Type of Retail Container - Indicate type of container in which product will be marketed.
3. Location of Net Contents - Indicate the location of the net contents information for your product.
4. Size(s) of Retail Container - Specify the net contents of all retail containers for your product.
5. Location of Use Directions - Indicate the location of the use directions for your product.
6. Manner in which label is affixed to product - Indicated the method product label is attached to retail container.

SECTION IV (Contact Point) - This Section must be completed for all applications for Registration actions, i.e., now products registration, resubmission, "me-too," reregistration, etc.

- 1-5. Self-explanatory.
6. EPA Use Only





United States
Environmental Protection Agency
Washington, DC 20460

☐ Registration
☐ Amendment
☐ Other

OPP Identifier Number

277150

Application for Pesticide - Section I

| | | |
|--|--|---|
| 1. Company/Product Number | 2. EPA Product Manager | 3. Proposed Classification <input type="checkbox"/> None <input type="checkbox"/> Restricted |
| 4. Company/Product (Name) | PM# | |
| 5. Name and Address of Applicant (Include ZIP Code) <input type="checkbox"/> Check if this is a new address | 6. Expedited Review. In accordance with FIFRA Section 3(c)(3) (b)(i), my product is similar or identical in composition and labeling to: EPA Reg. No. _____ Product Name _____ | |

Section - II

| | |
|--|--|
| <input type="checkbox"/> Amendment - Explain below. | <input type="checkbox"/> Final printed labels in response to Agency letter dated _____ |
| <input type="checkbox"/> Resubmission in response to Agency letter dated _____ | <input type="checkbox"/> "Me Too" Application. |
| <input type="checkbox"/> Notification - Explain below. | <input type="checkbox"/> Other - Explain below. |

Explanation: Use additional page(s) if necessary. (For section I and Section II.)

Section - III

| | | | | | |
|---|---|--|--|---|--|
| 1. Material This Product Will Be Packaged In: | | | | 2. Type of Container | |
| Child-Resistant Packaging <input type="checkbox"/> Yes <input type="checkbox"/> No | Unit Packaging <input type="checkbox"/> Yes <input type="checkbox"/> No | Water Soluble Packaging <input type="checkbox"/> Yes <input type="checkbox"/> No | | <input type="checkbox"/> Metal | |
| | | | | <input type="checkbox"/> Plastic | |
| | | | | <input type="checkbox"/> Glass | |
| | | | | <input type="checkbox"/> Paper | |
| | | | | <input type="checkbox"/> Other (Specify) _____ | |
| 3. Location of Net Contents Information <input type="checkbox"/> Label <input type="checkbox"/> Container | | 4. Size(s) Retail Container | | 5. Location of Label Directions <input type="checkbox"/> On Label <input type="checkbox"/> On Labeling accompanying product | |
| 6. Manner in Which Label is Affixed to Product <input type="checkbox"/> Lithograph <input type="checkbox"/> Paper glued <input type="checkbox"/> Stenciled | | <input type="checkbox"/> Other _____ | | | |

Section - IV

| | | |
|---|----------|--|
| 1. Contact Point (Complete items directly below for identification of individual to be contacted, if necessary, to process this application.) | | |
| Name | Title | Telephone No. (Include Area Code) |
| Certification I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law. | | 6. Date Application Received (Stamped) |
| 2. Signature | 3. Title | |
| 4. Typed Name | 5. Date | |

PAPERWORK REDUCTION ACT NOTICE and INSTRUCTIONS

PAPERWORK REDUCTION ACT NOTICE: Public reporting burden for this collection of information is estimated to average 0.85 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding the burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Chief, Information Policy Branch, (2136), U.S. Environmental Protection Agency, 401 M Street, SW, Washington, DC 20460.

INSTRUCTIONS: This form is to be used for all applications for new registration, and use reregistration, amendment, resubmission, to applications for notifications, final printed labeling, reregistration, etc. In order to process an application for a new registration submitted on this form, the following material must accompany the application:

1. Certification with Respect to Citation of Data (EPA Form 8570-29). [If not exempted by 40 CFR 152.81 (b) (4)];
2. Confidential Statement of Formula (EPA Form 8570-4);
3. Formulator's Exemption Statement (EPA Form 8570-27);
4. Five copies of draft labeling;
5. Three copies of any data submitted;
6. Authorization letter where applicable;
7. Matrices where applicable.

Submission of Labeling - Labeling should first be submitted in the form of draft labels with all applications for new registration. Such draft labels may be in the form of typed label text on 8.5 x 11 inch paper for submission or a mockup of the proposed label. If prepared for mockup, it should be constructed in a way as to facilitate storage in an 8.5 x 11 inch file. Mockup labels significantly smaller than 8.5 x 11 inches should be mounted on 8.5 x 11 inch paper for submission.

Submission of Data - Data submitted in support of this application must be submitted in accordance with PR Notice 86-5.

SPECIFIC INSTRUCTIONS: Please read the instructions listed below before completing this application. First determine the type of registration action, listed in Block A, for which you are submitting this application. For applications submitted in connection with New Registration actions, Sections I, III, and IV must be completed by the applicant. For applications submitted in connection with amended reregistration actions, resubmissions, notifications, reregistrations, etc., Sections I, II, and IV must be completed by the applicant.
Block A - Check the appropriate action for which you are submitting this form.

SECTION I - This section must be completed, as applicable, for all registration actions.

1. **Company/Product Number** - Insert your Company Number, if one has been assigned by EPA. This number may have been assigned to you as a basic registrant, a distributor, or as an establishment. If your product is registered, insert the Product Number.
2. **EPA Product Manager** - If known, fill in the name and PM number of the EPA Product Manager.
3. **Proposed Classification** - Specify the proposed classification of this product.
4. **Product Name** - Enter the complete product name of this pesticide as it will appear on the label. The name must be specific to this product only. Duplication of names is not permitted among products of the same company. Do not include any brand name or company line designations.
5. **Name and Address of Applicant** - The name of the firm or person and address shown in your application is the person or firm to whom the registration will be issued. If you are acting in behalf of another party, you must submit authorization from that party to act for them in registration matters. An applicant not residing in the United States must have an authorized agent residing in the United States to act for them in all registration matters. The name and complete mailing address of such an agent must accompany this application.
6. **Expedited Review** - FIFRA section 3 (c) 3 (B) provides for expedited review of applications for registration, or amendments to existing registrations, that are similar or identical to other pesticide products that are currently registered with the EPA. In order for your application to be eligible for expedited review, you must provide us with the EPA Registration Number and product name of the product you believe is similar to or identical to your product. The product must be similar or identical in both formulation and labeled uses.

SECTION II - This section must be completed for all applications submitted to amend the registration only of a currently registered product (Amendment), for a resubmission in response to an Agency letter, for notifications to the Agency, for the submission of final printed labeling, for reregistration and for any other action that pertains to a specific EPA-registered product. This section is not to be used for a new application for registration.

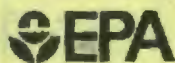
1. **Subject of submission** - Check the applicable block and provide the Agency letter date if appropriate. Provide a brief explanation of the purpose(s) for the submission, such as "the addition of a site, pest or crop (specify)"; "amend the Confidential Statement of Formula by..."; "reregistration submission"; "general label revision of use directions." Attach a separate page if additional space is needed.

SECTION III (Packaging and Container Information) - This Section must be completed for all applications submitted in connection with new registration or applicable amendments.

1. **Type of Packaging** - Check the appropriate block if your product will be packaged in the indicated packaging types. Indicate the size of the individual packets and number per retail container.
2. **Type of Retail Container** - Indicate type of container in which product will be marketed.
3. **Location of Net Contents** - Indicate the location of the net contents information for your product.
4. **Size(s) of Retail Container** - Specify the net contents of all retail containers for your product.
5. **Location of Use Directions** - Indicate the location of the use directions for your product.
6. **Manner in which label is affixed to product** - Indicate the method product label is attached to retail container.

SECTION IV (Contact Point) - This Section must be completed for all applications for Registration actions, i.e., new products registration, resubmission, "me-too," reregistration, etc.

- 1-5. Self-explanatory.
6. EPA Use Only.



United States
Environmental Protection Agency
Washington, DC 20460

☐ Registration
☐ Amendment
☐ Other

OPP Identifier Number

277150

Application for Pesticide - Section I

| | | |
|--|--|---|
| 1. Company/Product Number | 2. EPA Product Manager 03 | 3. Proposed Classification <input type="checkbox"/> None <input type="checkbox"/> Restricted |
| 4. Company/Product (Name) | PM# | |
| 5. Name and Address of Applicant (Include ZIP Code) <input type="checkbox"/> Check if this is a new address | 6. Expedited Review. In accordance with FIFRA Section 3(c)(3) (b)(i), my product is similar or identical in composition and labeling to: EPA Reg. No. _____ Product Name _____ | |

Section - II

| | |
|--|--|
| <input type="checkbox"/> Amendment - Explain below. | <input type="checkbox"/> Final printed labels in response to Agency letter dated _____ |
| <input type="checkbox"/> Resubmission in response to Agency letter dated _____ | <input type="checkbox"/> "Me Too" Application. |
| <input type="checkbox"/> Notification - Explain below. | <input type="checkbox"/> Other - Explain below. |

Explanation: Use additional page(s) if necessary. (For section I and Section II.)

Section - III

| | | | | | |
|---|---|--|--|---|--|
| 1. Material This Product Will Be Packaged In: | | | | 2. Type of Container | |
| Child-Resistant Packaging <input type="checkbox"/> Yes* <input type="checkbox"/> No | Unit Packaging <input type="checkbox"/> Yes <input type="checkbox"/> No | Water Soluble Packaging <input type="checkbox"/> Yes <input type="checkbox"/> No | | <input type="checkbox"/> Metal | |
| | | | | <input type="checkbox"/> Plastic | |
| | | | | <input type="checkbox"/> Glass | |
| | | | | <input type="checkbox"/> Paper | |
| | | | | <input type="checkbox"/> Other (Specify) _____ | |
| 3. Location of Net Contents Information <input type="checkbox"/> Label <input type="checkbox"/> Container | | 4. Size(s) Retail Container | | 5. Location of Label Directions <input type="checkbox"/> On Label <input type="checkbox"/> On Labeling accompanying product | |
| 6. Manner in Which Label is Affixed to Product <input type="checkbox"/> Lithograph <input type="checkbox"/> Paper glued <input type="checkbox"/> Stenciled | | <input type="checkbox"/> Other _____ | | | |

Section - IV

| | | | |
|--|--|-----------------------------------|---|
| 1. Contact Point (Complete items directly below for identification of individual to be contacted, if necessary, to process this application.) | | | |
| Name | | Title | |
| | | Telephone No. (Include Area Code) | |
| Certification I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law. | | | 8. Date Application Received (Stamped) |
| 2. Signature | | 3. Title | |
| 4. Typed Name | | 5. Date | |

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INSTRUCTIONS: This form is to be used for all applications for new registration, end use reregistration, amendment, resubmission, to applications for notifications, final printed labeling, reregistration, etc. In order to process an application for a new registration submitted on this form, the following material must accompany the application:

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7. Matrices where applicable.

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SPECIFIC INSTRUCTIONS: Please read the instructions listed below before completing this application. First determine the type of registration action, listed in Block A, for which you are submitting this application. For applications submitted in connection with New Registration actions, Sections I, III, and IV must be completed by the applicant. For applications submitted in connection with amended reregistration actions, resubmissions, notifications, reregistrations, etc., Sections I, II, and IV must be completed by the applicant.

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4. **Product Name** - Enter the complete product name of this pesticide as it will appear on the label. The name must be specific to this product only. Duplication of names is not permitted among products of the same company. Do not include any brand name or company line designations.
5. **Name and Address of Applicant** - The name of the firm or person and address shown in your application is the person or firm to whom the registration will be issued. If you are acting in behalf of another party, you must submit authorization from that party to act for them in registration matters. An applicant not residing in the United States must have an authorized agent residing in the United States to act for them in all registration matters. The name and complete mailing address of such an agent must accompany this application.
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1. **Subject of submission** - Check the applicable block and provide the Agency letter date if appropriate. Provide a brief explanation of the purpose(s) for the submission, such as "the addition of a site, pest or crop (specify)"; "amend the Confidential Statement of Formula by..."; "reregistration submission"; "general label revision of use directions." Attach a separate page if additional space is needed.

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5. **Location of Use Directions** - Indicate the location of the use directions for your product.
6. **Manner in which label is affixed to product** - Indicate the method product label is attached to retail container.

SECTION IV (Contact Point) - This Section must be completed for all applications for Registration actions, i.e., new products registration, resubmission, "me-too," reregistration, etc.

- 1-5. Self-explanatory.
6. EPA Use Only.



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

June 11, 2001

I, Thomas Harris, Insecticide/Rodenticide Branch, Registration Division, Office of Pesticide Programs, Office of Prevention, Pesticides and Toxic Substances, United States Environmental Protection Agency ("EPA"), certify that the pesticide product (s) listed below is, as of the date of this letter, a registered product under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended, and that as such, the product(s) may be sold and marketed in the United States of America as authorized and limited by FIFRA. A true and correct copy of the product label approved by EPA is attached to accompany this letter.

Registration of this product(s) with EPA also denotes that the registrant listed below is responsible for ensuring full compliance with all the laws of the United States of America, or governing jurisdiction, regarding the sale, storage and/or disposal of the product(s). Further, the recipient of this letter is on notice that the referenced registration and/or the accompanying label may change subsequent to the date of this letter. EPA assumes no responsibility to notify the recipient of this letter of any change in the status of the registration(s) and/or the product label for the product(s) listed below.

EPA has issued registration numbers for the product(s) listed below to:

Syngenta Crop Protection, Inc.
P.O. Box 18300
Greensboro, NC 27419-8300

EPA Registration Number:
Name of Product:

100-902
Enamectin Benzoate Technical

Thomas Charles Harris
Chemical Manager
Insecticide/Rodenticide Branch
Registration Division (7505C)





May 15, 2001

Ms. Tina Levine, Chief
Insecticide-Rodenticide Branch, Registration Division
Office of Pesticide Programs (7505C)
U.S. Environmental Protection Agency
Ariel Rios Building
1200 Pennsylvania Ave. NW
Washington, DC 20460

Dear Ms. Levine:

SUBJECT: REQUEST FOR CERTIFICATES OF REGISTRATION

Our Syngenta colleagues in other countries to whom Syngenta Crop Protection, Inc. U.S. supplies product, require Certificates of Registration (gold seals) for those products to satisfy their individual country's registration requirements. Please provide us with three Certificates of Registration for the following product(s):

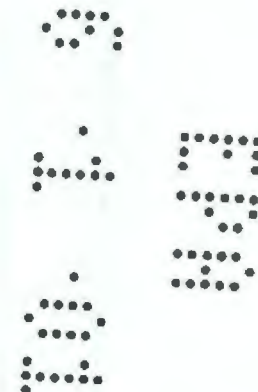
| <u>Name of Product</u> | <u>EPA Reg. No.</u> |
|------------------------------|---------------------|
| Enamectin Benzoate Technical | 100-902 |

To meet the registration timelines in the requesting countries, please provide the Certificates of Registration as soon as possible. If you have any questions about this request, please contact me at the below telephone number. Thank you for your time and assistance.

Sincerely,

Sharon Waynick
Regulatory Support Team
Regulatory Affairs
PH 336-632-7930

cc: Registration Authentication File
Chron





UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUN 1 2001

Carolyn Brinkley
Syngenta Crop Protection, Inc.
PO Box 18300
Greensboro, NC 27419

re: Eamectin Benzoate Technical, EPA Reg. # 100-902
revised basic CSF and new product chemistry submitted 7/19/99
accepted

Dear Ms. Brinkley:

The Agency has reviewed your submission for a revised Confidential Statement of Formula (CSF). The Confidential Statement of Formula dated 5/18/99 for the basic formulation is acceptable. Revised ingredients were found to be similar to previous ingredients. The ingredient percentages and limits comply with PR Notice 91-2. The basic Confidential Statement of Formula have been added to your file as part of the record. This replaces all previous versions.

The Agency has also reviewed new product chemistry data (MRID 448837-01 to -05). This submission meets the data requirements as specified in 40CFR158.162 with respect to description of the production process. This submission also satisfies the data requirement as specified in 40CFR158.190 with respect to physical and chemical characteristics for pH (830.7000), n-octanol/water partition coefficient (830.7570), water solubility (830.7840), and the calculation of Henry's Law Constant (not required). Enclosed please find a copy of the review by B. Kitchens dated 11/30/00.

The revised basic CSF and additional data satisfy all data gaps identified in a previous product chemistry review (DP Barcode 192197 review by A. Smith dated 7/9/93).

If you have any questions please contact me at (703) 308-9423 or
harris.thomas@epa.gov.

Yours truly,

A handwritten signature in black ink, appearing to be "TH", is located below the "Yours truly," text.

Thomas C. Harris, Biologist
Insecticide-Rodenticide Branch
Registration Division (7505C)

enclosure

DATE OUT: 30 Nov 2000

SUBJECT: EP [x] MP [] PRODUCT CHEMISTRY REVIEW

DP BARCODE No.: D267360

REG./File Symbol No.: 100-902

PRODUCT NAME: Emamectin Benzoate Technical

COMPANY: Norvartis Crop Protection, Inc.

TO: PM #04, Tina Levine/Tom Harris
Insecticide-Rodenticide Branch
Registration Division (7505C)

FROM: Bruce F. Kitchens, Chemist
Technical Review Branch
Registration Division (7505C)

Bruce F. Kitchens
30 Nov 2000

prod chem

INTRODUCTION:

The registrant, Norvartis Crop Protection, Incorporated, is submitting additional data requested in a previous product chemistry review (DP Barcode 192197 09 July 1993). In that review, it was determined that data regarding solubility, stability, and pH for the EP & TGAI must be submitted at the time of registration. Additionally, a new CSF for the TGAI must be submitted in which impurities at levels of 0.1% must be identified on the CSF. All other product chemistry data requirements were satisfied. With this submission, the registrant is submitting data the following data:

1. Description of Production Process (40 CFR 158.162) MRID# 448837-01
2. pH of Water Solutions or Suspensions (830.7000) MRID# 448837-02
3. n-Octanol/Water Partition Coefficient (830.7570) MRID# 448837-03
4. Water Solubility (830.7840) MRID# 448837-04
5. Henry's Law Constant MRID# 448837-05

The active ingredient in this product is Emamectin Benzoate at 96% a.i. and is intended for use as an insecticide manufacturing use product. With this request, the registrant has submitted a basic Confidential Statement of Formula dated 18 May 1999, a label, and product chemistry data contained in MRID#s 448837-01 through 448837-05. The Technical Review Branch (TRB) has been asked to review this submission.

SUMMARY OF FINDINGS:

TRB has reviewed this submission and reports the following findings:

1. The study entitled: Description of Production Process (40 CFR 158.162) MRID# 448837-01 is acceptable. The production process is completely and thoroughly described.
2. The study entitled: pH of Water Solutions or Suspensions (830.7000) MRID# 448837-02 is acceptable. The average pH of a 1% by weight aqueous suspension at 25°C was determined to be 6.4.
3. The study entitled: n-Octanol/Water Partition Coefficient (830.7570) MRID# 448837-03 is acceptable. The log P_{ow} was determined by liquid chromatography. The n-octanol/water partition coefficient for the major component Emamectin Benzoate B_{1a} was determined to be 5.7. The n-octanol/water partition coefficient for the minor component Emamectin Benzoate B_{1b} was determined to be 5.2.
4. The study entitled: Water Solubility (830.7840) MRID# 448837-04 is acceptable. The solubility of Emamectin Benzoate's major and minor components (B_{1a} and B_{1b}) were determined in water and in pH 5, 7, and 9 buffer solutions at 21°C using the flask method. The average, $B_{1a} + B_{1b}$, solubilities were 105 mg/l in water, 101 mg/l in pH 5.0 buffer solution, and 93 mg/l in pH 7.0 buffer solution. No peaks were detected in pH 9.0 buffer solution since Emamectin Benzoate has limited stability under alkaline conditions.
5. The data calculation as presented in the study Henry's Law Constant MRID# 448837-05 is acceptable. Henry's Law Constant was calculated to be 3.80×10^{-12} atm·m³/mole.

CONCLUSIONS:

TRB has reviewed this submission and concludes the following:

1. The basic CSF dated 18 May 1999 is acceptable.
2. This submission meets the data requirements as specified in 40 CFR 158.162 with respect to description of the production process.
3. This submission also satisfies the data requirement as specified in 40 CFR 158.190 with respect to physical and chemical characteristics for pH (830.7000), n-Octanol/Water partition coefficient (830.7570), Water Solubility (830.7840), and the calculation of Henry's Law Constant (not required).

MEMORANDUM

~~6/30/93~~
5/4/94 from HED due files

SUBJECT: PP#3G4239 -- Merck and Co., Inc., MK-0244 (Emamectin Benzoate) for Use in/on Cole Crops and Leafy Vegetables. Petition Dated June 30, 1993. DP Barcode: D194566, CBTS # 12439. MRID #'s: 427436-44, 427436-45, 427436-46, 427436-47, 427436-48, 427436-49, 427436-50, 427436-51, 427942-02, 428515-20, 428515-21, 428515-22, 428515-25, 428689-03, 428689-04.

FROM: Michael T. Flood, Ph.D., Chemist
Tolerance Petition Section II
Chemistry Branch I -- Tolerance Support
Health Effects Division (7509C)

*reference prod chem
review D 192197*

THROUGH: Elizabeth T. Haeberer, Section Head, TPSII
Chemistry Branch I -- Tolerance Support
Health Effects Division (7509C)

TO: George LaRocca, PM 13
Insecticide - Rodenticide Branch
Registration Division (7505C)

Attached please find the review of Merck and Co, Inc.'s temporary tolerance petition/EUP for use of MK-0244 [4"-deoxy-4"-epi-methyl amino avermectin B1 benzoate] in/on cole crops and leafy vegetables. These studies were reviewed by Dynamac Corporation. The review has undergone secondary review in CBTS and has been revised to be consistent with Branch policies.

CBTS does not recommend that temporary tolerances be established for this pesticide. The analytical method must be independently validated and a question concerning the analytical method must be answered. The petitioner must submit revised Sections B and F in which the proposed use/tolerance is limited to "head lettuce" instead of "lettuce".

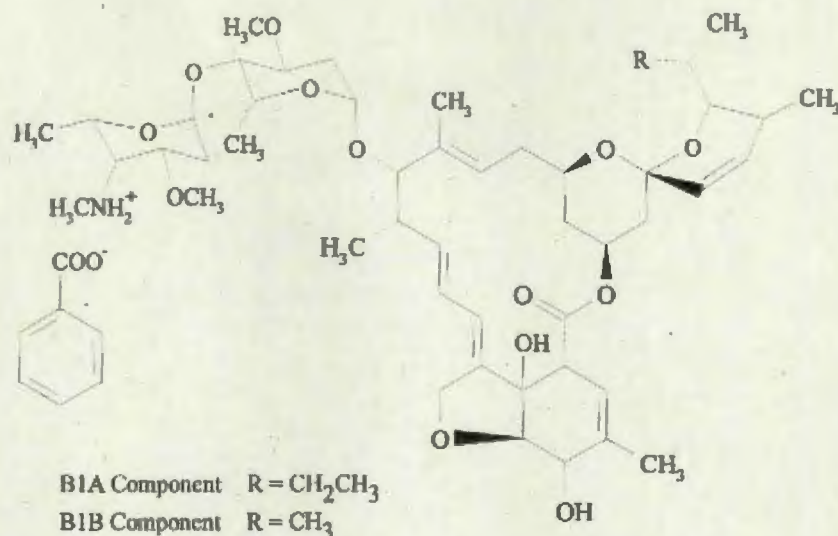
Attachment (with 5 sub-attachments): Dynamac Corporation review dated 2/18/94.

cc(with attachments): PP#3G4239, Mike Flood, RF, SF.

cc(without sub-attachments): Circu.

cc(without attachment or sub-attachments): E. Haeberer.

7509C:CBTS:Reviewer(MTF):CM#2:Rm804P:703-305-7990:typist(mtf):4/26/94.
RDI:SectionHead:ETHaeberer:4/20/94:BranchSeniorScientist:RALoranger:
4/22/94:BranchChief:DFEdwards:4/25/94MK-0244



TEMPORARY TOLERANCE PETITION (PP#3G04239)

AND EXPERIMENTAL USE PERMIT FOR USE OF MK-0244

ON COLE CROPS AND LEAFY VEGETABLES

(CBTS NO. 12439; DP BARCODE NO. D194566)

INTRODUCTION

MK-0244 [4"-deoxy-4"-epi-methyl amino avermectin B1 benzoate (proposed common name = emamectin benzoate)] is a broad spectrum larvicide/insecticide developed by Merck and Co., Inc. as a second generation semi-synthetic avermectin. MK-0244 is derived from abamectin and is a mixture of two homologues designated as B1A (or MAB1A) and B1B (or MAB1B) typically present at a ratio of 90:10 (MAB1A:MAB1B).

The petitioner, Merck and Co., Inc., is proposing the establishment of temporary tolerances for the combined residues of MK-0244, its delta 8,9-isomer, and the degradation products, 4"-deoxy-4"-epi-(N-formyl)-avermectin B1a (FAB1A), 4"-deoxy-4"-epi-(N-formyl-N-methyl)-avermectin B1a (MFB1A), and 4"-deoxy-4"-epi-amino avermectin B1a (AB1A) as follows:

| | |
|-----------------------|-----------|
| Broccoli..... | 0.025 ppm |
| Brussels Sprouts..... | 0.025 ppm |
| Cabbage..... | 0.025 ppm |
| Cauliflower..... | 0.025 ppm |
| Celery..... | 0.025 ppm |
| Lettuce..... | 0.025 ppm |

No temporary or permanent tolerance has yet been established for residues of MK-0244 and its metabolites and degradation products in/on raw agricultural and animal commodities.

Associated with this temporary tolerance petition, Merck has requested an experimental use permit (EUP) for use of MK-0244 EC (EPA File Symbol No. 618-EUP-RU) on cole crops (broccoli, Brussels sprouts, cabbage, and cauliflower) and leafy vegetables (celery and lettuce). The primary purpose of this EUP is to further define and obtain crop residue and efficacy data from large plots using commercial ground boom application equipment. The EUP program involves use of 50 acres in AZ, southern CA, FL, and south TX. The total quantity of material proposed for use is 109 quarts of formulated product (4.5 lb ai equivalent).

CONCLUSIONS

1. The product chemistry data submitted with this petition are adequate to fulfill the requirements for this EUP and temporary tolerance request. The comments listed in Attachment I are intended to aid the petitioner in fulfilling the requirements for a future permanent tolerance.
- 2a. The nature of the residue in plants is adequately understood for purposes of this EUP and temporary tolerance petition. CBTS tentatively concludes that the residue of concern is parent compound MK-0244, its delta 8,9-isomer, and the degradation products FAB1A, MFB1A and AB1A. The significance of the remaining metabolites that were identified (each at level <0.01 ppm, each $\leq 3\%$ TRR) following exaggerated (6.7x) rates will be deferred to the HED Metabolism Committee. The Committee will also determine which compounds must appear in the tolerance expression.
- 2b. For establishment of permanent tolerances, the nature of the residue in plants is not adequately understood. The petitioner should attempt to further characterize/identify the unknown polar ^{14}C -residues in the methanol:water extracts of lettuce leaf. These polar residues accounted for up to 0.105 ppm ($\sim 55\%$ TRR) from 1.3x-treated lettuce and 0.328 ppm ($\sim 55\%$ TRR) from 6.7x-treated lettuce. The polar residues should at least be further characterized in a manner similar to the polar fractions found in the avermectin B₁ metabolism studies. Assuming that complete chromatographic separation of these metabolites is not likely, the petitioner should at least demonstrate that the polar fraction does not consist of compounds having the macrocyclic lactone ring.
- 2c. At this time no further work need be done on the DMSO-extractable residue or the residue remaining after DMSO extraction. However, for permanent tolerances, the petitioner should confirm that the residues remaining after methanol:water extraction were extracted with DMSO, then extracted with methanol, then extracted with DMSO -- as stated on page 40. Elsewhere (page 52) it is implied that methanol was used to partially solubilize the residue already extracted by DMSO, not the residue remaining after DMSO extraction.
- 2d. Assuming that further characterization of the polar residues gives results analogous to those for avermectin B₁, CBTS will not require an additional metabolism study on cole crops. (This

conclusion could change if forthcoming studies on additional crops demonstrate dissimilar metabolic profiles.)

3. No animal metabolism or feeding studies were submitted with this petition. However, tolerances in milk, eggs, and animal tissues are not needed since no feed items are associated with the subject commodities for which temporary tolerances are being proposed.
4. The available data indicate that Method 244-92-3, with a detection limit of 0.001 ppm for each analyte, is adequate for determining residues of MK-0244 and its metabolites (MFB1A, 8,9-Z, AB1A, and FAB1A) in/on leafy vegetable and cole crop commodities. Method 244-92-3 is adequate for residue data collection only. For purposes of this EUP and temporary tolerance petition, an independent laboratory method validation, in accordance with PR Notice 88-5 dated 7/15/88, is required. The structure of the fluorescent derivative should be submitted.

For the establishment of permanent tolerances, ACB/BEAD will perform a petition method validation (PMV) once a successful independent laboratory validation has been conducted. CBTS reiterates that the proposed enforcement method must be radiovalidated using representative samples from the lettuce metabolism study. Finally, MK-0244 and the other compounds appearing in the tolerance expression should be tested using FDA's Multiresidue methods (PAM Vol. I).

5. For purposes of this EUP and temporary tolerance petition, the submitted storage stability data are adequate. The data indicate that residues of MK-0244 and its metabolites are stable in/on lettuce and cabbage under frozen storage conditions for up to 3 months.

For establishment of permanent tolerances, additional storage stability data are required reflecting the maximum storage intervals of samples from the magnitude of the residue studies in broccoli (~6 months), cabbage (~5 months), celery (~17 months), and head lettuce (~28 months). CBTS is aware that the final report of an ongoing three-year storage stability study will be submitted when completed.

- 6a. For purposes of this EUP and temporary tolerance petition, the available data indicate that combined residues of MK-0244 and its metabolites (delta 8,9-isomer; FAB1A; MFB1A; and AB1A) will not exceed the proposed tolerances of 0.025 ppm in/on celery and head lettuce following applications of the 0.16 lb/gal EC formulation according to the proposed use patterns (7-day PHI; six foliar applications at 0.015 lb ai/A/application; 7-day retreatment intervals). CBTS is unable to draw a similar conclusion concerning leaf lettuce. A revised Section F should be submitted in which the proposed tolerance is for head lettuce only. A revised Section B should also be submitted in which use is limited to head lettuce.
- 6b. For establishment of permanent tolerances, additional field residue data are required. For celery, field trial data depicting residues of concern are needed from an additional five trials conducted in Region X and from one trial conducted in Region V. (A list of states within a region is given in Attachment V to this memo.) If the petitioner wishes to obtain a tolerance for head lettuce only,

two additional field trials should be carried out in Region X. For a permanent tolerance for lettuce, as opposed to head lettuce, data depicting residues of concern on leaf lettuce are needed. At least six trials should be carried out in Region X (4 trials), Region III (1 trial) and Region I (1 trial).

- 7a. For purposes of this EUP and temporary tolerance petition, the available data indicate that combined residues of MK-0244 and its metabolites (delta 8,9-isomer; FAB1A; MFB1A; and AB1A) will not exceed the proposed tolerances of 0.025 ppm in/on broccoli, cabbage, and cauliflower following applications of the 0.16 lb/gal EC formulation according to the proposed use patterns (7-day PHI; six foliar applications at 0.015 lb ai/A/application; 7-day retreatment intervals).
- 7b. For establishment of permanent tolerances, additional field trials are required. The petitioner has the option of seeding tolerances for each RAC independently, in which case a total of 13 additional field trials would be necessary, or seeding crop group tolerances. Establishment of a crop group tolerance for Brassica leafy vegetables [40 CFR 180.34] would require an additional 9 trials. Establishment of a crop group tolerance for the forthcoming "head and stem Brassica" subgroup would require an additional 4 trials. These requirements are outlined in greater detail on pages 31-32 of this memo.
8. An International Residue Limit Status sheet is appended to this review. There are currently no Codex, Canadian, or Mexican maximum residue limits on MK-0244 or its metabolites. Compatibility is therefore not an issue.

RECOMMENDATIONS

CBTS cannot recommend in favor of this EUP and temporary tolerance request until the petitioner addresses the concerns relating the need for independent laboratory method validation (see Conclusion No. 4). The structure of the fluorescent derivative should be submitted. The petitioner must submit a revised Section F in which the proposed tolerance for "lettuce" is changed to "head lettuce" (Conclusion 6a). Pending decisions from the HED Metabolism Committee regarding what compounds should be regulated, the petitioner may have to submit an amended Section F (see Conclusion 2a). The other deficiencies cited are intended to aid the petitioner in fulfilling the requirements for future permanent tolerances.

DETAILED CONSIDERATIONS

Product Chemistry

The evaluation of product chemistry data (MRIDs 427436-44 through -51, and 42794202) associated with the EUP application was performed by RD (DP Barcode 192197, A. Smith, 7/9/93). The review addressed the product chemistry data requirements for MK-0244 Technical (TGAI) and MK-0244 EC

Insecticide (End-Use Product, EP). A complete copy of the review is included in this document as Attachment I (including Confidential Appendix containing CBI).

The following product chemistry topics were deemed adequate for both TGAI and EP: (i) product identity and disclosure of ingredients (GLN 61-1); (ii) beginning materials and manufacturing process (GLN 61-2); (iii) discussion of the formation of impurities (GLN 61-3); (iv) preliminary analysis (GLN 62-1); and (v) analytical methods to verify certified limits (GLN 62-3).

The certification of ingredient limits (GLN 62-2) was deemed adequate for the EP but not for the technical product. When full registration is requested, a Confidential Statement of Formula (CSF) for the TGAI must be submitted. Additionally, impurities present at levels of 0.1% should be identified and included on the CSF.

The submitted data on physical and chemical properties (GLNs 63-2 through 63-13) were also deemed adequate. However, when full registration is requested, the following additional data must be submitted: (i) solubility (both EP and TGAI); (ii) stability (TGAI); and (iii) pH (both EP and TGAI).

Proposed Use

MK-0244 EC (EPA File Symbol No. 618-EUP-RU) is an emulsifiable formulation containing 0.16 lb ai/gal and the following ingredients:

| | | |
|-------------------|--|--------|
| Active Ingredient | MK-0244: 4"-deoxy-4"-epi-methyl amino avermectin B1 benzoate (a mixture of a minimum of 90% 4"-deoxy-4"-epi-methyl amino avermectin B1A (25- <u>sec</u> -butyl) and a maximum of 10% 4"-deoxy-4"-epi- methyl amino avermectin B1B (25- <u>iso</u> -propyl) benzoate | 2.15% |
| Inert Ingredient | see Attachment I | 97.85% |

The product is proposed for six foliar applications to broccoli, Brussels sprouts, cabbage, cauliflower, celery, and lettuce at 0.0075-0.015 lb ai/A/application with a non-ionic surfactant using ground or aerial equipment with 7-day retreatment intervals. The proposed maximum seasonal rate per growing season is 0.09 lb ai/A. Aerial applications are to be made in a minimum of 5 gal/A. A grazing restriction and a 7-day PHI are proposed.

According to our updated Table II of the Residue Chemistry Guidelines, none of these commodities are animal feed items. The petitioner may wish to delete any grazing restriction from the label.

Qualitative Nature of the Residue in Lettuce

Merck and Co., Inc. submitted two volumes of data (1993; MRID 42851522) depicting the metabolism of [¹⁴C]MAB1A homolog of MK-0244 in head lettuce. The in-life phase of the study was initiated in 1990 and was conducted by ABC Laboratories, Inc. (Columbia, MO). The test substance, radiolabeled at one of five positions (C3, C7, C11, C13, or C23), was prepared as the EC formulation, diluted with water,

DP BARCODE: D267360

CASE: 046738
SUBMISSION: S582204

DATA PACKAGE RECORD
BEAN SHEET

DATE: 07/11/00
Page 1 of 1

* * * CASE/SUBMISSION INFORMATION * * *

CASE TYPE: REGISTRATION ACTION: 400 DATA-MISC DATA-NOT REQUES
RANKING : 15 POINTS ()
CHEMICALS: 122806 4''-Epimethylamino-4''-deoxyavermectin B1a and B1b 95.0000%

ID#: 000100-00902 EMAMECTIN BENZOATE TECHNICAL
COMPANY: 000100 NOVARTIS CROP PROTECTION, INC.
PRODUCT MANAGER: 04 TINA LEVINE 703-308-7055 ROOM: CM2 219
PM TEAM REVIEWER: THOMAS HARRIS 703-308-9423 ROOM: CM2 211
RECEIVED DATE: 07/22/99 DUE OUT DATE: 10/19/00

* * * DATA PACKAGE INFORMATION * * *

DP BARCODE: 267360 EXPEDITE: N DATE SENT: 07/11/00 DATE RET.: / /
CHEMICAL: 122806 4''-Epimethylamino-4''-deoxyavermectin B1a and B1b benzoate
DP TYPE: 001

CSF: Y LABEL: Y
ASSIGNED TO DATE IN DATE OUT ADMIN DUE DATE: 12-11-00
DIV : RD / / / /
BRAN: TRB / / / /
SECT: ~~IR~~ chem / / / /
REVR : / / / /
CONTR: / / / /
NEGOT DATE: 10/29/00
PROJ DATE: / /

* * * DATA REVIEW INSTRUCTIONS * * *

Please review new product chemistry and revised basic CSF.
MRIDs: 448837 -01 thru -05

These were submitted in response to a request from CDPR (see p. 2 of Novartis 7/19/99 letter). Not sure why CDPR wanted it; differences in CSF are not obvious (except maybe product density and pH).

Copy of original prod chem review by HED is enclosed (it's part of analysis for temporary tolerance on cole crops).

Sorry for the delay in beaning this out; it was buried in a tolerance submission that just got on OPP workplan.

-Tom Harris

RD/IRB
308-9423

* * * DATA PACKAGE EVALUATION * * *

No evaluation is written for this data package

* * * ADDITIONAL DATA PACKAGES FOR THIS SUBMISSION * * *

| DP BC | BRANCH/SECTION | DATE OUT | DUE BACK | INS | CSF | LABEL |
|-------|----------------|----------|----------|-----|-----|-------|
|-------|----------------|----------|----------|-----|-----|-------|

See page 2 of letter for
CSF reference

Remaining data (see also
crit 4/8/99)
AUG 3 1999

U.S. ENVIRONMENTAL PROTECTION AGENCY
Office of Pesticide Programs

NOVARTIS CROP PROTECTION, INC.
P.O. BOX 18300
GREENSBORO, NC 274198300

Report of Analysis for Compliance with PR Notice 86-5

Thank you for your transmittal of 07/22/99. Our staff has completed a preliminary analysis of the material. The results are provided as follows:

Your submittal was found to be in full compliance with the standards for submission of data contained in PR Notice 86-5. A copy of your bibliography is enclosed, annotated with Master Record ID's (MRIDs) assigned to each document submitted. Please use these numbers in all future references to these documents. Thank you for your cooperation. If you have any questions concerning this data submission, please raise them with the cognizant Product Manager, to whom the data have been released.



Novartis Crop Protection, Inc.
P.O. Box 18300
Greensboro, NC 27419-8300
www.cp.us.novartis.com

Tel 336 632 6000

July 19, 1999

448837-00

Document Processing Desk (AMEND)
Office of Pesticide Programs (7504C)
U.S. Environmental Protection Agency
401 M Street S.W.
Washington, DC 20460

Attention: Mr. Thomas Harris, IRB

SUBJECT: EMAMECTIN BENZOATE, EPA REG. NO, 100-902, PROCLAIM®,
EPA REG. NO, 100-904, AND DENIM™ EPA REG. NO, 100-903:
AMENDED PETITION PP 7F4845 FOR TOLERANCES OF
EMAMECTIN BENZOATE IN OR ON FRUITING VEGETABLES,
LEAFY *BRASSICA* VEGETABLES, COTTON, AND LEAFY
VEGETABLES

Dear Mr. Harris,

Enclosed with this letter is the amended Pesticide Petition for the establishment of tolerances of emamectin benzoate fruiting vegetables, leafy *Brassica* vegetables, cotton, and leafy vegetables. In addition, Novartis requests amendment of the Proclaim and Denim labels to add these new use sites. Novartis also submits a Reduced Risk rationale for this petition for the Agency's consideration. Novartis believes emamectin benzoate is an excellent candidate for expedited review based on its organophosphate pesticide replacement possibilities.

The combination of new residue studies on leafy vegetables with previously acceptable residue studies on celery and head lettuce allow for the establishment of the proposed leafy vegetable tolerance. The establishment of the crop group tolerance will require the revocation or conversion of existing tolerances for head lettuce and celery.

Novartis Crop Protection lists this petition as a Number 13, minor use priority, in a letter dated 3/26/99.

Novartis also submits a draft summary of the Notice of Filing as required by FQPA for Federal Register publication and also copies of the label containing the new uses.

Along with the Residue Chemistry data volumes, Novartis is submitting several Product Chemistry volumes and a revised CSF for emamectin benzoate technical. Novartis generated these data as a response to reviews received from the California Department of Pesticide Regulation (CDPR). CDPR has reviewed the data base for emamectin benzoate in the process of registering the products in California. No significant results were noted in this data.

The proposed emamectin benzoate tolerances are below.

| Crop | Proposed Tolerance (ppm) | Crop | Proposed Tolerance (ppm) |
|----------------------------------|--------------------------|------------------------|--------------------------|
| Cottonseed | 0.025 | Cotton gin by-products | 0.05 |
| Fruiting Vegetables | 0.02 | Leafy Vegetables | 0.1 |
| Leafy <i>Brassica</i> Vegetables | 0.025 | | |

A check in the amount of \$4,100 will be sent to the EPA Headquarters Accounting Operations Branch to pay the required fees in association with the additional tolerance requested in this pesticide petition.

Thank you for your consideration of this petition. If you have any questions, please contact me at (336) 632-2391.

Sincerely,



Robert E. M. Wurz, Ph.D.
Senior Regulatory Manager
Regulatory Affairs

Enclosures:
Petition
Labels
Form 8570-1
CSF

**VOLUME 1 OF 24 OF SUBMISSION
(TRANSMITTAL DOCUMENT)**

1. NAME AND ADDRESS OF SUBMITTER

NOVARTIS CROP PROTECTION, INC.
P.O. BOX 18300
GREENSBORO, NC 27419

**2. REGULATORY ACTION IN SUPPORT OF WHICH THIS PACKAGE IS
SUBMITTED**

EMAMECTIN BENZOATE, EPA REG. NO. 100-902; AMENDED PETITION
PP7E4845 FOR TOLERANCES ON FRUITING VEGETABLES, LEAFY
BRASSICA VEGETABLES, COTTON, AND LEAFY VEGETABLES

3. TRANSMITTAL DATE

7/19/99

4. LIST OF SUBMITTED STUDIES

| MRID NUMBER | VOLUME NUMBER | STUDY TITLE | EPA GUIDELINE NUMBER |
|----------------|------------------|--|----------------------------|
| | 1 OF 24 | TRANSMITTAL DOCUMENT | NOT APPLICABLE |
| 44883701 | 2 OF 24 | EMAMECTIN BENZOATE TECHNICAL - PRODUCT CHEMISTRY; GROUP A; STUDY NO. PC-99-016; (387)(109186) | 830-1620 |
| 44883702 | 3 OF 24 | EMAMECTIN BENZOATE TECHNICAL (ADDENDUM TO MRID # 42794202); PRODUCT CHEMISTRY; GROUP B; (387)(886-99, 108552) | 830-7000 |
| 44883703 | 4 OF 24 | EMAMECTIN BENZOATE TECHNICAL (ADDENDUM TO MRID # 42794202); PRODUCT CHEMISTRY; GROUP B; (387)(163-98, 108553) | 830-7570 |

| MRID NUMBER | VOLUME NUMBER | STUDY TITLE | EPA GUIDELINE NUMBER |
|----------------|------------------|--|----------------------------|
| 44883704 | 5 OF 24 | EMAMECTIN BENZOATE TECHNICAL (ADDENDUM TO MRID # 42794202); PRODUCT CHEMISTRY; GROUP B; (387)(162-98, 108555) | 830-7840 |
| 44883705 | 6 OF 24 | EMAMECTIN BENZOATE TECHNICAL (ADDENDUM TO MRID 42794202); PRODUCT CHEMISTRY; GROUP B; STUDY NO. PC-99- 017; (387)(108554) | 830-7950 |
| 44883706 | 7 OF 24 | CGA-293343 AND EMAMECTIN - MAGNITUDE OF THE RESIDUE IN OR ON TOBACCO; (387)(133-98, 110078) | 860-1000, 860- 1500 |
| 44883707 | 8 OF 24 | EMAMECTIN - MAGNITUDE OF THE RESIDUES IN OR ON REPRESENTATIVE COMMODITIES OF CROP GROUP 4: LEAFY VEGETABLES; (387)(135-98, 110067) | 860-1000, 860- 1500 |
| 44883708 | 9 OF 24 | EMAMECTIN - MAGNITUDE OF THE RESIDUES IN OR ON REPRESENTATIVE COMMODITIES OF CROP GROUP 5: BRASSICA (COLE) LEAFY VEGETABLES; (387)(136-98, 110068) | 860-1000, 860- 1500 |
| 44883709 | 10 OF 24 | EMAMECTIN - MAGNITUDE OF THE RESIDUES IN OR ON REPRESENTATIVE COMMODITIES OF CROP GROUP 8: FRUITING VEGETABLES; (387)(137-98, 110069) | 860-1000, 860- 1500 |

| MRID NUMBER | VOLUME NUMBER | STUDY TITLE | EPA GUIDELINE NUMBER |
|----------------|------------------|--|----------------------------|
| 44883710 | 11 OF 24 | THE ELIMINATION, TISSUE DISTRIBUTION AND METABOLISM OF [³ H]4"-DEOXY-4"-EPIMETHYLAMINO AVERMECTIN B _{1A} (MAB _{1A}) BENZOATE AND [³ H/ ¹⁴ C] MAB _{1A} BENZOATE IN LACTATING GOATS; STUDY NO. ARM-9; (387)(522-94, 110277) | 860-1300 |
| 44883711 | 12 OF 24 | THE ELIMINATION, TISSUE DISTRIBUTION AND METABOLISM OF ³ H/ ¹⁴ C"-DEOXY-4"-EPIMETHYLAMINO AVERMECTIN B _{1A} (MAB _{1A}) BENZOATE IN LAYING CHICKENS; STUDY NO. ABR-97116 (MERCK #94706); (387)(477-96, 70285) | 860-1300 |
| 44883712 | 13 - 16 OF 24 | METHOD VALIDATION OF THE HPLC-FLUORESCENCE METHOD TO DETERMINE RESIDUES OF MK-0244 AND ITS 8,9-Z ISOMER IN BOVINE TISSUES, MILK, AND PLASMA; STUDY NO. 1031-99; (387)(1031-99, 110513) | 860-1340 |
| 44883713 | 17 OF 24 | INDEPENDENT LABORATORY VALIDATION FOR THE DETERMINATION OF EMAMECTIN BENZOATE (MK-0244) RESIDUES IN BOVINE LIVER TISSUE AND MILK; STUDY NO. MERCK NO. 94731; (387)(1033-99, 110515) | 860-1340 |

| MRID NUMBER | VOLUME NUMBER | STUDY TITLE | EPA GUIDELINE NUMBER |
|----------------|------------------|---|----------------------------|
| 44883714 | 18 - 22 OF 24 | A STUDY IN LACTATING COWS TO DETERMINE TISSUE, MILK AND PLASMA RESIDUES IN ANIMALS EXPOSED TO TWENTY-EIGHT DAYS OF ORAL INGESTION OF MK-0244 (EMAMECTIN BENZOATE); STUDY NO. MERCK 94401; (387)(1032-99, 110543) | 860-1480 |
| 44883715 | 23 OF 24 | DETERMINATION OF THE MAGNITUDE OF RESIDUES OF MK-244 AND ITS METABOLITES IN/ON THE RAW AGRICULTURAL COMMODITY GROUP, FRUITING VEGETABLES, FROM MK-244 5 SG APPLIED WITH A NON-IONIC SURFACTANT BY GROUND EQUIPMENT; STUDY NO. MERCK NO. 618-244-94461; (387)(1013-99, 110511) | 860-1500 |
| 44883716 | 24 OF 24 | CGA-293343 + EMAMECTIN - MAGNITUDE OF THE RESIDUES IN OR ON COTTON; (387)(132-98, 110077) | 860-1500, 860-1520 |

COMPANY OFFICIAL: WURZ, ROBERT E
(NAME)


(SIGNATURE)

COMPANY NAME: NOVARTIS CROP PROTECTION, INC.

COMPANY CONTACT: WURZ, ROBERT E
(NAME)

(336)632-2321
(PHONE)



United States
Environmental Protection Agency
Washington, DC 20460

☐ Registration
☐ Amendment
☒ Other

OPP Identifier Number
NOTIFICATION

Application for Pesticide - Section I

| | | |
|---|--|--|
| 1. Company/Product Number 100-902 | 2. EPA Product Manager Tom Harris | 3. Proposed Classification <input checked="" type="checkbox"/> None <input type="checkbox"/> Restricted |
| 4. Company/Product (Name) Emamectin Benzoate Technical | PM# IRB | |
| 5. Name and Address of Applicant (Include ZIP Code) Syngenta Crop Protection, Inc. P. O. Box 18300 Greensboro, NC 27419 <input type="checkbox"/> Check if this is a new address | 6. Expedited Review. In accordance with FIFRA Section 3(c)(3) (b)(i), my product is similar or identical in composition and labeling to: EPA Reg. No. _____ Product Name _____ | |

Section - II

- ☐ Amendment - Explain below. ☐ Final printed labels in response to Agency letter dated _____
- ☐ Resubmission in response to Agency letter dated _____ ☐ "Me Too" Application.
- ☒ Notification - Explain below. ☐ Other - Explain below.

NOTIFICATION

MAR 21 2001

Explanation: Use additional page(s) if necessary. (For Section I and Section II.)

This notification is consistent with the provisions of PR Notice 98-10 and EPA regulations at 40 CFR 152.46, and no other changes have been made to the labeling or the confidential statement of formula of this product. I understand that it is a violation of 18 U.S.C. Sec. 1001 to willfully make any false statement to EPA. I further understand that if this notification is not consistent with the terms of PR Notice 98-10 and 40 CFR 152.46, this product may be in violation of FIFRA and I may be subject to enforcement action and penalties under sections 12 and 14 of FIFRA. The following changes are being made via this notification: 1) Company name and address have been updated to reflect Syngenta Crop Protection, Inc. 2) The Conditions of Sale and Warranty statement has been changed to reflect the name change. Because Syngenta has been formed by the merger of Novartis Crop Protection, Inc. and Zeneca Ag Products, we have chosen to use the former Zeneca warranty statement as the Syngenta warranty statement. No other changes occur in the statement other than the name change. 3) The copyright date reflects Syngenta. 4) Trademark statements have been updated to reflect Syngenta for those products for which Syngenta holds the trademark. 5) The Internet address has been changed to reflect Syngenta. 6) Other places in the label which referring to the company name have been updated.

Section - III

| | | | | | |
|---|---|--|--|---|--|
| 1. Material This Product Will Be Packaged In: | | | | 2. Type of Container | |
| Child-Resistant Packaging <input type="checkbox"/> Yes* <input type="checkbox"/> No | Unit Packaging <input type="checkbox"/> Yes <input type="checkbox"/> No | Water Soluble Packaging <input type="checkbox"/> Yes <input type="checkbox"/> No | | <input type="checkbox"/> Metal | |
| Certification must be submitted | | | | <input type="checkbox"/> Plastic | |
| If "Yes" Unit Packaging wgt. No. per Container | | If "Yes" Unit Packaging wgt. No. per container | | <input type="checkbox"/> Glass | |
| | | | | <input type="checkbox"/> Paper | |
| | | | | <input type="checkbox"/> Other (Specify) _____ | |
| 3. Location of Net Contents Information <input type="checkbox"/> Label <input type="checkbox"/> Container | | 4. Size(s) Retail Container | | 5. Location of Label Directions <input type="checkbox"/> On Label <input type="checkbox"/> On Labeling accompanying product | |
| 6. Manner in Which Label is Affixed to Product <input type="checkbox"/> Lithograph <input type="checkbox"/> Paper glued <input type="checkbox"/> Stenciled | | | | <input type="checkbox"/> Other _____ | |

Section - IV

| | | | |
|--|--|--|--|
| 1. Contact Point (Complete items directly below for identification of individual to be contacted, if necessary, to process this application) | | | |
| Name Nan S. Padgett | | Title Label Group Leader | |
| | | Telephone No. (Include Area Code) 226-632-7567 | |
| 2. Signature <i>Nan S. Padgett</i> | | 3. Title Label Group Leader | |
| 4. Typed Name Nan S. Padgett | | 5. Date March 12, 2001 | |
| I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law. | | 6. Date Application Received (Stamped) STG 5/10/01 | |

NOTIFICATION

MAR 21 2001

Emamectin Benzoate Technical

An Insecticide For Formulation Use Only

Active Ingredients:

| | |
|---|-------|
| Emamectin Benzoate* (4"-epi-methylamino-4"- deoxyavermectin B ₁ benzoate) | 96.0% |
| Related Compounds | 3.0% |

| | |
|--------------------|------|
| Inert Ingredients: | 1.0% |
|--------------------|------|

| | |
|--------|--------|
| Total: | 100.0% |
|--------|--------|

*CAS No. 137512-74-4

Made in U.S.A.

EPA Reg. No. 100-902

EPA Est. 618-PA-1

Product ID. **184294**

KEEP OUT OF REACH OF CHILDREN.

DANGER/POISON



Lot # _____

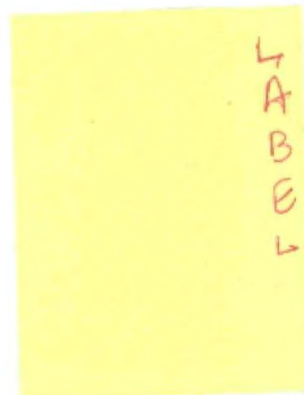
Net Weight:

Physical _____ Kg

Assay _____ Kg

Drum No. _____

Manu. ID 22763



syngenta



CONDITIONS OF SALE AND LIMITATION OF WARRANTY AND LIABILITY

NOTICE: Read the entire Directions for Use and Conditions of Sale and Limitation of Warranty and Liability before buying or using this product. If the terms are not acceptable, return the product at once, unopened, and the purchase price will be refunded.

The Directions for Use of this product should be followed carefully. It is impossible to eliminate all risks inherently associated with the use of this product. Crop injury, ineffectiveness or other unintended consequences may result because of such factors as manner of use or application, weather or crop conditions, presence of other materials or other influencing factors in the use of the product, which are beyond the control of SYNGENTA CROP PROTECTION, Inc. or Seller. All such risks shall be assumed by Buyer and User, and Buyer and User agree to hold SYNGENTA and Seller harmless for any claims relating to such factors.

SYNGENTA warrants that this product conforms to the chemical description on the label and is reasonably fit for the purposes stated in the Directions for Use, subject to the inherent risks referred to above, when used in accordance with directions under normal use conditions. This warranty does not extend to the use of the product contrary to label instructions, or under abnormal conditions or under conditions not reasonably foreseeable to or beyond the control of Seller or SYNGENTA, and Buyer and User assume the risk of any such use. SYNGENTA MAKES NO WARRANTIES OF MERCHANTABILITY OR OF FITNESS FOR A PARTICULAR PURPOSE NOR ANY OTHER EXPRESS OR IMPLIED WARRANTY EXCEPT AS STATED ABOVE.

In no event shall SYNGENTA or Seller be liable for any incidental, consequential or special damages resulting from the use or handling of this product. **THE EXCLUSIVE REMEDY OF THE USER OR BUYER, AND THE EXCLUSIVE LIABILITY OF SYNGENTA AND SELLER FOR ANY AND ALL CLAIMS, LOSSES, INJURIES OR DAMAGES (INCLUDING CLAIMS BASED ON BREACH OF WARRANTY, CONTRACT, NEGLIGENCE, TORT, STRICT LIABILITY OR OTHERWISE) RESULTING FROM THE USE OR HANDLING OF THIS PRODUCT, SHALL BE THE RETURN OF THE PURCHASE PRICE OF THE PRODUCT OR, AT THE ELECTION OF SYNGENTA OR SELLER, THE REPLACEMENT OF THE PRODUCT.**

SYNGENTA and Seller offer this product, and Buyer and User accept it, subject to the foregoing conditions of sale and limitations of warranty and of liability, which may not be modified except by written agreement signed by a duly authorized representative of SYNGENTA.

DIRECTIONS FOR USE

It is a violation of Federal law to use this product in a manner inconsistent with its labeling.

This product may be used only to manufacture/formulate other insecticide products registered and labeled for use on head and stem Brassica crops, celery, and head lettuce.

STORAGE AND DISPOSAL

Storage

Store in a tightly closed original container in a cool, dry place.

Pesticide Disposal

Pesticide wastes are acutely hazardous. Improper disposal of excess pesticide, spray mixture, or rinsate is a violation of federal law. If these wastes cannot be disposed of by the use according to label instructions, contact your State Pesticide or Environmental Control Agency, or the Hazardous Waste representative at the nearest EPA Regional Office for guidance.

Container Disposal

Triple rinse (or equivalent). Then offer for recycling or reconditioning, or puncture and dispose of in a sanitary landfill, or by other procedures approved by state and local authorities.

PRECAUTIONARY STATEMENTS

Hazards to Humans and Domestic Animals

DANGER

Corrosive. Causes irreversible eye damage. Do not get in eyes or on clothing. Wear protective eyewear (goggles, face shields, or safety glasses). May be fatal if swallowed. Wash thoroughly with soap and water after handling and before eating, drinking, or using tobacco. Remove contaminated clothing and wash clothing before reuse.

Recommendations for Medical Treatment for Emamectin Benzoate Acute Toxicity: Early signs of intoxication include mydriasis (dilated pupils), ataxia (unsteadiness), and muscle tremors. Toxicity following accidental ingestion of the concentrate can be minimized by inducing vomiting within 1/2 hour of exposure. If toxicity from exposure has progressed to cause severe vomiting, the extent of resultant fluid and electrolyte imbalance should be gauged. Appropriate supportive parenteral fluid replacement therapy should be given, along with other required supportive measures (such as maintenance of blood pressure levels) as indicated by clinical signs, symptoms, and measurements. In severe cases, observations should continue for at least several days until clinical condition is stable and normal. Since emamectin benzoate is believed to enhance GABA activity in animals, it is probably wise to avoid drugs that enhance GABA activity (barbiturates, benzodiazepines, valproic acid) in patients with potentially toxic emamectin benzoate exposure.

For 24 hour emergency medical information, call Syngenta Crop Protection, Inc. at 1-800-888-8372.

Emamectin Benzoate Technical

Statement of Practical Treatment

If in eyes: Hold eyelids open and flush with a steady, gentle stream of water for 15 minutes. Get medical attention.

If swallowed: Call a doctor or get medical attention. Do not induce vomiting or give anything by mouth to an unconscious person. Drink promptly a large quantity of milk, egg whites, gelatin solution, or, if these are not available, drink large quantities of water. Avoid alcohol.

If on skin: Wash with plenty of soap and water. Get medical attention.

If inhaled: Remove victim to fresh air. If not breathing, give artificial respiration, preferably mouth-to-mouth. Get medical attention.

Environmental Hazards

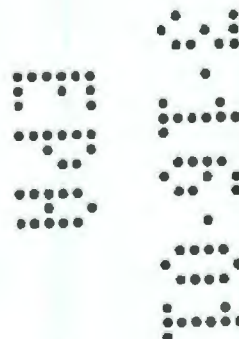
This pesticide is toxic to fish, birds, mammals, and aquatic invertebrates. Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans, or other waters, unless in accordance with the requirements of a National Pollutant Discharge Elimination System (NPDES) permit and the permitting authority has been notified in writing prior to discharge. Do not discharge effluent containing this product to sewer systems without previously notifying the local sewage treatment plant authority. For guidance, contact your State Water Board or Regional Office of the EPA.

The labeling of any product formulated from this product must state: "This product is highly toxic to bees exposed to direct treatment or residues on blooming crops or weeds. Do not apply this product or allow drift to blooming crops or weeds if bees are visiting the treatment area."

©2001 Syngenta

Syngenta Crop Protection, Inc.
Greensboro, North Carolina 27409
www.syngenta-us.com

SCP 902A-L1D 0201





Certified Mail

March 12, 2001

Document Processing Desk (NOTIF)
Office of Pesticide Programs (H7504C)
U.S. Environmental Protection Agency
Ariel Rios Building
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Attn: Ms. Sherada Hobgood (RD)

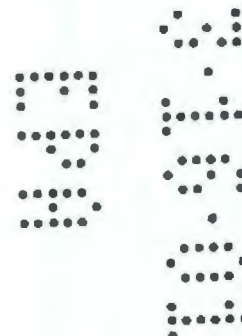
Dear Ms. Hobgood:

**SUBJECT: EMAMECTIN BENZOATE TECHNICAL
EPA REG. NO. 100-902
NOTIFICATION OF NAME CHANGE TO SYNGENTA CROP PROTECTION, INC.**

Enclosed is one copy of the subject product label which includes the following changes: [Note: Although a change in company name and address according to PR Notice 98-10 Part IV D. does not require a notification to the Agency as long as the ownership of the registration has been officially changed, Syngenta is submitting this notification to aid in state registration. In addition, the use of the former Zeneca warranty statement (see below) on former Novartis products, we believe, constitutes the need for a notification.]

1. Company name and address have been updated to reflect Syngenta Crop Protection, Inc.
2. The Conditions of Sale and Warranty statement has been changed to reflect the name change. Because Syngenta has been formed by the merger of Novartis Crop Protection, Inc. and Zeneca Ag Products, we have chosen to use the former Zeneca warranty statement as the Syngenta warranty statement. No other changes occur in the statement other than the name change.
3. The copyright date reflects Syngenta.
4. Trademark statements have been updated to reflect Syngenta for those products for which Syngenta holds the trademark.
5. The Internet address has been changed to reflect Syngenta.
6. Other places in the label which referring to the company name have been updated.

All of the above changes have been highlighted in the copy of labeling provided.





March 12, 2001
Ms. Sherada Hobgood
Notification of Company Name Change

To complete this notification, an EPA Form 8570-1 is included as well.

If you have any questions regarding this notification, please feel free to contact me at 336 632 7567.

Thank you for handling this matter.

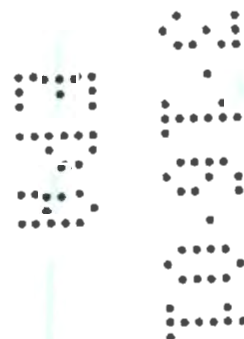
Sincerely,

A handwritten signature in dark ink that reads "Nan Padgett". The signature is written in a cursive, flowing style.

Nan Padgett
Labeling Group Lead
Regulatory Affairs

Enclosures

cc: Tom Harris, Team IRB (only letter)





Certified Mail

March 12, 2001

Document Processing Desk (NOTIF)
Office of Pesticide Programs (H7504C)
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Ariel Rios Building
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

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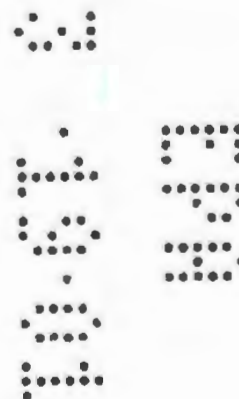
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March 12, 2001
Ms. Sherada Hobgood
Notification of Company Name Change

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If you have any questions regarding this notification, please feel free to contact me at 336-632-7567.

Thank you for handling this matter.

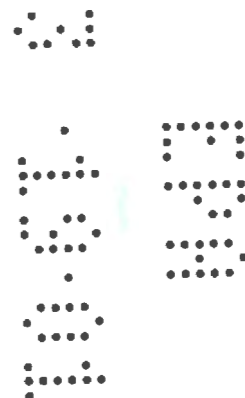
Sincerely,

A handwritten signature in black ink that reads "Nan Padgett". The signature is written in a cursive, flowing style.

Nan Padgett
Labeling Group Lead
Regulatory Affairs

Enclosures

cc: Tom Harris, Team IRB (only letter)





UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Original
hand delivered
to Dick

NOV 10 1999

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Dick Feulner
Novartis Crop Protection, Inc.
P.O. Box 18300
Greensboro, NC 27419-8300

Re: OP Alternative Status for Uses of New Emamectin Benzoate on Fruiting Vegetables, Head and Stem Brassica Vegetables, Leafy Brassica Vegetables, Leafy Vegetables, Cotton, and Tobacco

Dear Dick,

Thank you for your request to have the Agency re-consider the insecticide, emamectin benzoate, as an OP alternative for new uses on fruiting vegetables, head and stem brassica vegetables, leafy brassica vegetables, leafy vegetables, cotton, and tobacco. This letter is a written confirmation of the Agency's decision to grant emamectin benzoate OP alternative status only, for these uses. This decision was made by the reduced risk committee on November 1, 1999. As you know, the Agency previously denied emamectin benzoate reduced risk status (the only status requested by your company at the time) on August 10, 1999. This decision stands and emamectin benzoate is not a reduced risk chemical for these proposed uses.

Please note that the OP alternative status of any chemical is an initial assessment. Should information warrant, the Agency may re-evaluate and possibly revoke your submission's OP alternative status. Also, should the Agency determine at any time that the data base for the chemical is unacceptable or incomplete, the Agency may stop the expedited process for the chemical until adequate data are submitted.

As a result of the decision to designate these uses as an OP alternative, the Agency will begin working with its science divisions to schedule the data reviews and risk assessments needed for evaluating this chemical. The Agency has a goal of completing these evaluations in an expeditious manner. Tina Levine, Chief of the Insecticide-Rodenticide Branch, will now handle all regulatory issues associated with this application. Tina can be reached at (703) 308-7055.

Thank you for your interest in reduced risk pesticides. If you have any questions regarding the reduced risk pesticide program please feel free to contact Alan Dixon at (703) 305-7237.

Sincerely yours,



Rick Keigwin, Chief
Registration Support Branch
Registration Division (7505C)

cc: Tina Levine
Thomas Harris

This document will publish in the
FEDERAL REGISTER of 10-4-99.
Approximately 24 hours after
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(NE Mall G-304).

John A. Richards, Director
Federal Register Staff

Dir Rd Rm 711 7505C

332

ENVIRONMENTAL PROTECTION AGENCY

[OPP-30414A; FRL-6385-1]

Pesticide Product Registrations; Conditional Approval

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: This notice announces Agency approval of applications submitted by Novartis Crop Protection Inc., to conditionally register the pesticide products Emamectin Benzoate Technical, Denim Insecticide, and Proclaim Insecticide, products containing a new active ingredient not included in any previously registered products pursuant to the provisions of section 3(c)(7)(C) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended.

FOR FURTHER INFORMATION CONTACT: By mail: Linda Arrington, Registration Division (7505C), Office of Pesticide Programs, Environmental Protection Agency, 401 M St., SW., Washington, DC 20460; telephone number: 703-305-5446; and e-mail address: arrington.linda@epa.gov.

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this Action Apply to Me?

You may be affected by this action if you are an agricultural producer, food manufacturer, or pesticide manufacturer. Potentially affected categories and entities may include, but are not limited to:

| Categories | NAICS codes | Examples of potentially affected entities |
|------------|----------------------------|---|
| Industry | 111 112 311 32532 | Crop production Animal production Food manufacturing Pesticide manufacturing |

This listing is not intended to be exhaustive, but rather provides a guide for readers regarding entities likely to be affected by this action. Other types of entities not listed in the table could also be affected. The North American Industrial Classification System (NAICS) codes have been provided to assist you and others in determining whether or not this action might apply to certain entities. If you have questions regarding the applicability of this action to a particular entity, consult the person listed in the "FOR FURTHER INFORMATION CONTACT."

B. How Can I Get Additional Information, Including Copies of this Document and Other Related Documents?

1. *Electronically.* You may obtain electronic copies of this document, and certain other related documents that might be available electronically, from the EPA Internet Home Page at <http://www.epa.gov/>. To access this document, on the Home Page select "Laws and Regulations" and then look up the entry for this document under the "Federal Register--Environmental Documents." You

can also go directly to the **Federal Register** listings at <http://www.epa.gov/fedrgstr/>.

To access a fact sheet which provides more detail on this registration, go to the home page for the Office of Pesticide Programs at <http://www.epa.gov/pesticides/>, and select "factsheet."

2. *In person.* The Agency has established an official record for this action under docket control number OPP-30414A. The official record consists of the documents specifically referenced in this action, any public comments received during an applicable comment period, and other information related to this action, including any information claimed as Confidential Business Information (CBI). This official record includes the documents that are physically located in the docket, as well as the documents that are referenced in those documents. The public version of the official record does not include any information claimed as CBI. The public version of the official record, which includes printed, paper versions of any electronic comments submitted during an applicable comment period, is available for inspection in the Public Information and Records Integrity Branch (PIRIB), Rm. 119, Crystal Mall #2, 1921 Jefferson Davis Hwy., Arlington, VA, from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The PIRIB telephone number is (703) 305-5805.

In accordance with section 3(c)(2) of FIFRA, a copy of the approved label, the list of data references, the data and other scientific information used to support registration, except for material specifically protected by section 10 of FIFRA, are available for public inspection in the Public Information and Records Integrity Branch, Information Resources and Services Division (7502C), Office of Pesticide Programs, Environmental Protection Agency, Rm. 119, Crystal Mall #2, Arlington, VA ((703) 305-5805). Requests for data must be made in accordance with the provisions of the Freedom of Information Act and must be addressed to the Freedom of Information Office (A-101), 401 M St., SW., Washington, DC 20460. Such requests should: Identify the product name and registration number and specify the data or information desired.

A paper copy of the fact sheet, which provides more detail on this registration, may be obtained from the National Technical Information Service (NTIS), 5285 Port Royal Road, Springfield, VA 22161.

II. Did EPA Conditionally Approve the Application(s)?

A conditional registration may be granted under section 3(c)(7)(C) of FIFRA for a new active ingredient where certain data are lacking, on condition that such data are received by the end of the conditional registration period and do not meet or exceed the risk criteria set forth in 40 CFR 154.7; that use of the pesticide during the conditional registration period will not cause unreasonable adverse effects; and that use of the pesticide is in the public interest. The Agency has considered the available data on the risks associated with the proposed use of emamectin benzoate, and information on social, economic, and environmental benefits to be derived from such use. Specifically, the Agency has considered the nature and its pattern of use, application methods and rates, and level and extent of potential exposure. Based on these reviews, the Agency was able to

make basic health and safety determinations which show that use of emamectin benzoate during the period of conditional registration will not cause any unreasonable adverse effect on the environment, and that use of the pesticide is, in the public interest.

Consistent with section 3(c)(7)(C) of FIFRA, the Agency has determined that these conditional registrations are in the public interest. Use of the pesticides are of significance to the user community, and appropriate labeling, use directions, and other measures have been taken to ensure that use of the pesticides will not result in unreasonable adverse effects to man and the environment.

III. Conditionally Approved Registrations

EPA issued a notice, published in the **Federal Register** of July 10, 1996 (61 FR 36372)(FRL-5377-9), which announced that Merck Research Laboratories, P.O. Box 450 Hillsborough Rd., Three Bridges, NJ 0887-0450, had submitted applications to register the products Emamectin Benzoate Technical, Proclaim 0.26 EC Insecticide, and Proclaim 5 SG Insecticide (EPA File Symbols 618-RNI, 618-RNT, and 618-RNA) containing the active ingredient emamectin benzoate 4''-epi-methylamino-4''-deoxyavermectin B₁ benzoate [A mixture of a minimum of 90''-epi-methylamino-4''-deoxyavermectin B₁ and a maximum of 10''-epi-methylamino-4''-deoxyavermectin B₁ benzoate at 95%, 2.15%, and 5% respectively. The technical product is the only one containing emamectin benzoate and 4% of related compounds. These products were not previously registered.

These products were subsequently transferred to Novartis Crop Protection, Inc., P.O. Box 18300, Greensboro, NC 27419-8300, and were assigned new EPA Registration Numbers.

The applications were approved on May 19, 1999, for one technical and two end-use products:

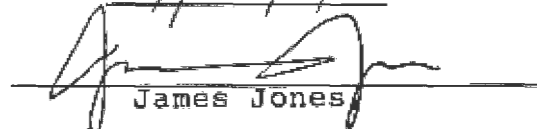
1. Emamectin Benzoate Technical for formulation use only (EPA Registration Number 100-902).
2. Denim Insecticide (formerly Proclaim 0.16 EC) for use on cavalo broccolo (EPA Registration Number 100-903).
3. Proclaim Insecticide for control of certain lepidopteran pests on head and stem *Brassica* vegetables, celery, and lettuce (EPA Registration Number 100-904).

Authority: 7 U.S.C. 136.

List of Subjects

Environmental protection, Pesticides and pests.


Dated: 9/23/99


James Jones

Director, Registration Division, Office of Pesticide Programs.

[FR Doc. 99-???? Filed ??-??-99; 8:45 am]

BILLING CODE 6560-50-F


Certified to be a true
copy of the original.



United States
Environmental Protection Agency
Washington, DC 20460

FEDERAL REGISTER TYPESETTING REQUEST

Requestor: Complete Items 1, 2, 7, 8, 9, 10, 11, 12 and 13. Retain copy number 7 and submit the balance with manuscript copy to the Hq. Federal Register Office.
HQ Federal Register Office: Complete Items 3, 4, 5 and 6. Retain copy number 6 and submit balance to Hq. Printing Management.

1. TITLE

OPP-30414A Approval of Applications Conditional

2. SUBMITTING ACTIVITY

3. ASSIGNED FRL NUMBER (include alpha & numeric characters for identification.)

6385-1

4. OPEN REQUISITION NUMBER

5. BILLING CODE

6. FORWARDED TO GSA, NARS - SIGNATURE

DATE

7. NUMBER OF MANUSCRIPT PAGES

8. ESTIMATED NUMBER OF COLUMNS

4

9. ESTIMATED COST

428

10. SIGNATURE: (a) REQUESTING OFFICER

11. SIGNATURE: (a) FEDERAL REGISTER DESIGNEE

(b) DATE

(c) TELEPHONE NUMBER

(b) DATE

(c) TELEPHONE NUMBER

9/27/89

305-6921

12. FUNDS ARE AVAILABLE

Priscilla Roberts

Priscilla Roberts

305-6921

NAME OF FUNDS CERTIFYING OFFICER

SIGNATURE OF FUNDS CERTIFYING OFFICER

PHONE NUMBER OF FUNDS CERTIFYING OFFICER

99P-1921

Emily

This document was submitted with electronic codes and is eligible for the 30% typesetting discount.

13. Financial and Accounting Data

| Line | DCN (Max 6) | Budget/FYs (Max 4) | Appropriation Code (Max 6) | Budget Org/Code (Max 7) | Program Element (Max 8) | Object Class (Max 4) |
|------|----------------|-----------------------|-------------------------------|----------------------------|----------------------------|-------------------------|
| 1 | EAC016 | 99/00 | B | 32200AF | 30103C | 2413 |
| 2 | | | | | | |
| 3 | | | | | | |

| Amount | (Dollars) | (Cents) | Site/Project (Max 6) | Cost Org/Code (Max 7) |
|--------|-----------|---------|-------------------------|--------------------------|
| 428.00 | | | | |
| | | | | |
| | | | | |

SFO

27

(Max 2)

ENVIRONMENTAL PROTECTION AGENCY

[OPP-30414A; FRL-6385-1]

Pesticide Product Registrations; Conditional Approval

AGENCY: Environmental Protection Agency (EPA).

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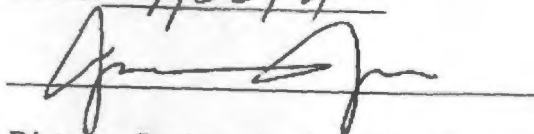
| | | | | | | | | |
|----------|-----------|---------|---------|--------------|--|--|--|--|
| 99P-1921 | | | | CONCURRENCES | | | | |
| SYMBOL | 7104 | 7104 | 7052 | | | | | |
| SURNAME | E. Glueck | | | | | | | |
| DATE | 9-20-99 | 9/20/99 | 9/22/99 | | | | | |

Authority: 7 U.S.C. 136.

List of Subjects

Environmental protection, Pesticides and pests.

Dated: 9/23/99



Director, Registration Division, Office of Pesticide Programs.

[FR Doc. 99-????? Filed ??-??-99; 8:45 am]

BILLING CODE 6560-50-F



May 19, 1999

Mr. George LaRocca
Office of Pesticide Programs H7504C
U.S. Environmental Protection Agency
401 M Street S.W.
Washington, DC 20460

Novartis Crop Protection, Inc.
P.O. Box 18300
Greensboro, NC 27419-8300
www.cp.us.novartis.com

Tel 336 632 6000

*George LaRocca
5/26/99*

*George - give Tia
a copy and
you should
send a copy
FVS to Jim Jones
also, Larry Turner
should get one.
Sharon
Lynch*

SUBJECT: EMAMECTIN BENZOATE: PP NO. 6F4628;
EMAMECTIN BENZOATE TECHNICAL, EPA REG. NO. 100-902
DENIM™, EPA REG. NO. 100-903
PROCLAIM™, EPA REG. NO. 100-904,
ENDANGERED SPECIES CONSIDERATIONS.

Dear Mr. LaRocca,

Novartis has reviewed a 5/10/99 memo from Larry Turner to George LaRocca regarding endangered species considerations for emamectin benzoate. In the memo, the Agency indicates that it would like additional proximity information on the Great Dismal Swamp shrew and the Nashville crayfish. The memo also notes that Novartis may satisfy the EPA needs for endangered species proximity data via membership in the Endangered Species Task Force (ESTF).

Novartis has been an active member of ESTF since inception and will continue to support it during the completion of the task force effort. As such, we intend to satisfy the emamectin data requirement through ESTF membership and efforts. However, Novartis recognizes the increased pressures on the EPA for quick resolution of endangered species issues related to pesticide registrations. Therefore, we will encourage the ESTF to prioritize data acquisition such that the information requested on the Great Dismal Swamp shrew and the Nashville crayfish are provided to the Agency as quickly as possible. This approach will be consistent with current EPA/ESTF and Fish & Wildlife agreements and hopefully also provide the data in a timely fashion.

If you have any questions or comments, please contact me at (336) 632-2391.

Sincerely,

Robert E. M. Wurz, Ph.D.
Senior Regulatory Manager
Regulatory Affairs

100-902

903

904





Novartis Crop Protection, Inc.
P.O. Box 18300
Greensboro, NC 27419-8300
www.cp.us.novartis.com

Tel 336 632 6000

May 3, 1999

Mr. George LaRocca
Office of Pesticide Programs H7504C
U.S. Environmental Protection Agency
401 M Street S.W.
Washington, DC 20460

SUBJECT: EMAMECTIN BENZOATE: PP NO. 6F4628;
EMAMECTIN BENZOATE TECHNICAL, EPA REG. NO. 100-902
DENIM™, EPA REG. NO. 100-903
PROCLAIM™, EPA REG. NO. 100-904,
NOVARTIS ACCEPTANCE OF CONDITIONAL REGISTRATION

Dear Mr. LaRocca,

Novartis has received the draft document outlining the conditional registrations of emamectin benzoate technical, Proclaim and Denim. The proposed registrations are conditional until 5/1/02 with two provisions for data submission to secure full registration. Novartis plans to fulfill both data requirements. Specifically, Novartis agrees to conduct or secure a waiver for an Estuarine/Marine Invertebrate Life-cycle Study (Guideline 72b) by 5/1/01. Novartis will also cooperate with EPA to revise or reissue, if necessary, the tolerance enforcement methodology for emamectin benzoate. If you have any questions or comments, please contact me at (336) 632-2391.

Sincerely,

Robert E. M. Wurz, Ph.D.
Senior Regulatory Manager
Regulatory Affairs



320/5562992
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MAY 24 1999

I, George T. LaRocca, Insecticide Branch, Registration Division, Office Of Pesticide Programs, Office of Prevention, Pesticide and Toxic Substances, United States Environmental Protection Agency (EPA), certify that the pesticide product(s) listed below is, as of the date of this letter, a registered product with EPA under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended and that as such, the product(s) may be sold and marketed in the United States of America as authorized and limited by FIFRA. A true and corrected copy of the product label approved by EPA is attached to accompany this letter.

Registration of this/these product(s) with EPA also denotes that the registrant listed below is responsible for ensuring full compliance with all laws of the United States of America, or governing jurisdiction, regarding the, sale, storage and/or disposal of the product(s). Further, the recipient of this letter is on notice that the status of the referenced registration and/or the accompanying label may change subsequent to the date of this letter. EPA assumes no responsibility to notify any recipient of this letter of any change in the status of the registration(s) and/or the product label for the product(s) listed below.

EPA has issued registration numbers for the product(s) listed below to:

NOVARTIS CROP PROTECTION, INC
Post Office Box 18300
Greensboro, North Carolina 27419-8300

EPA Registration Number
✓ 100-902
100-904

Product Name
EMAME CTIN BENZOATE Technical
PROCLAIM Insecticide

George T. LaRocca
Product Manager (13)
Insecticide Branch
Registration Division (7505C)

Enclosure

